Index Number

Vol. 228, No. 6 DECEMBER, 1954 No. 992

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

UNIVERSITY OF MICHIGAN
DEC 15 1954
HOSPITAL LIBRARY

REG. U. S. PAT. OFF.
ESTABLISHED 1820

Editor
RICHARD A. KERN, M.D.

Associate Editor
THOMAS M. DURANT, M.D.

Assistant Editor
CHRIS J. D. ZARAFONETIS, M.D

Carl Bachman, Herman Beerman, Wm. L. Benedict, A. M. Bongiovanni, George E. Burch, McKeen Cattell, Frank R. Drake, G. Lyman Duff, Franklin G. Ebaugh, Noah D. Fabricant, Harry Gold, John E. Gordon, David M. Gould, Theodore H. Ingalls, N. R. Ingraham, Jr., C. G. Johnston, E. G. D. Murray, A. Harry Neffson, Franklin L. Payne, I. S. Ravdin, C. Thorpe Ray, Robert D. Sloan, John H. Stokes, H. P. Wagener, Irving J. Wolman

Natural History, Functional Capacity and Exercise Tolerance of Unoperated Patients with Mitral Stenosis. By JAMES J. PAMPUSH, M.D., and ROBERT A. BRUCE, M.D. 605

The Effects of Intravenous Infusions of the Optical Isomers of Dibozane (McN-181;1,4-Bis [1,4-Benzodioxan-2-Ylmethyl] Piperazine), an Adrenergic Blocking Agent, Upon Hypertensive Subjects. By LOUIS B. KRAMER, M.D., ROBERT VAN HORNE, M.D., SAMUEL BELLET, M.D., and GEORGE B. KOELLE, PH.D., M.D. 614

The Cardiac Output of Normal Subjects Determined by the Dye-injection Method at Rest and During Exercise. By HENRY J. KOWALSKI, M.D., WALTER H. ABELMANN, M.D., WILLIAM F. MCNEELY, M.D., N. ROBERT FRANK, M.D., and LAURENCE B. ELLIS, M.D. 622

Long-term Intravenous Use of Arfonad in the Treatment of Pulmonary Edema. By LAMONT E. DANZIG, CAPT., MC, and ALPHONSE C. GOMEZ, 1ST LT., MC. 626

Stress and Gastric Secretion in Man. I. A Study of the Mechanisms Involved in Insulin Hypoglycemia. By HARRY SHAY, M.D., and DAVID C. H. SUN, M.D., M.Sc. 630

Simultaneous Pressure Measurements in the Hepatic Venule and Portal Venous System in Man. By GEORGE E. WELCH, M.D., ROBERT EMMETT, M.D., CLAUDE C. CRAIGHEAD, M.D., GEORGE HOEFFLER, M.D., DONOVAN C. BROWNE, M.D., and IRVING ROSEN, M.D. 643

N-Hydroxyethylethylenediamine Triacetic Acid, Versenol, in the Treatment of Hemochromatosis. By MARVIN J. SEVEN, 1ST LT., MC, USAR, HARRY GOTTLIEB, M.D., HAROLD L. ISRAEL, M.D., JOHN G. REINHOLD, PH.D., and MARTIN RUBIN, PH.D. 646

Lack of Effect of Fat Ingestion on Blood Coagulation. By PHIL R. MANNING, M.D., and ROY L. WALFORD, M.D. 652

Certain Observations on the Uptake of Base in Uremia and Acidosis due to Advanced Renal Disease. By RICHARD A. NEUBAUER, M.D. 656

Studies of Thyroid Function in Myotonia Dystrophica. By C. E. BENDA, M.D., C. J. MALETSKOS, PH.D., J. C. HUTCHINSON, M.D., and E. B. THOMAS, S.M. 668

Congenital Absence of a Main Branch of the Pulmonary Artery. By J. E. FLYNN, M.D., LT. (MC) USNR, A. A. SIEBENS, M.D., LT. (MC) USNR and S. F. WILLIAMS, M.D., CAPT. (MC) USN. 673

Progress of Medical Science

Pediatrics—Genetics in Pediatric Disease. By BARTON CHILDS, M.D. 680

Gynecology and Obstetrics—Carcinoma of the Endometrium. By ALFRED I. SHERMAN, M.D., and A. N. ARNESON, M.D. 701

Complete contents on adv. page 10

OWNERS AND PUBLISHERS LEA & FEBIGER PHILADELPHIA 6, PENNA.

Copyright, 1954, by Lea & Febiger. All Rights Reserved. Entered as second-class matter November 5, 1887 at the Post Office at Philadelphia, Pa. under the act of March 3, 1879

PUBLISHED MONTHLY. SUBSCRIPTIONS, TEN DOLLARS A YEAR

When Blood Pressure Soars to Dangerous Heights

You can depend on Hepvisc to reduce readings to safer levels, as well as to bring your patients gratifying relief from the subjective symptoms.

AVERAGE BLOOD PRESSURE BY AGE (Auscultatory Method)

AGE	Under 18	18-22	23-27	28-32	33-37	38-42	43-47	48-52	53-57	58-62	63 +
SYSTOLIC Male	117.0	120.2	121.2	121.8	122.9	124.3	126.0	128.1	130.3	131.9	134.2
Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

**Fourth phase
*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

···HEPVISC REG. U. S. PAT. OFF.

Hexanitrate of Mannitol + Viscum Album

Available in Bottles of 50-500-1000 tablets.
Complete Literature and Professional Samples Sent upon Request

THE ANGLO-FRENCH DRUG CO. (U.S.A.) LTD.
75 Varick St., New York 13, N. Y.

your patients get high blood levels in 2 hours or less

filmtab*

Erythrocin® STEARATE

(ERYTHROMYCIN STEARATE, ABBOTT)

disintegrates faster than enteric-coated erythromycin

filmtab*

Erythrocin . . . *for faster absorption*

New tissue-thin *Filmtab* coating (marketed only by Abbott) starts to disintegrate within 30 seconds—makes ERYTHROCIN Stearate available for immediate absorption. Tests show Stearate form definitely protects drug from stomach acids.

filmtab*

Erythrocin . . . *for earlier blood levels*

because there's no delay from an enteric coating, patients get high, inhibitory blood levels of ERYTHROCIN *in less than 2 hours*—instead of 4-6 as before. Peak concentration is reached at 4 hours, with significant levels for 8 hours.

filmtab*

Erythrocin . . . *for your patients*

Filmtab ERYTHROCIN Stearate is highly effective against coccic infections . . . and especially useful when the infecting coccus is resistant to other antibiotics. Low in toxicity—*it's less likely to alter normal intestinal flora than most other oral antibiotics.* Conveniently sized (100 and 200 mg.) in bottles of 25 and 100. Abbott

**TM for Abbott's film sealed tablets, pat. applied for.*

412231

CONTENTS

ORIGINAL ARTICLES

Natural History, Functional Capacity and Exercise Tolerance of Unoperated Patients with Mitral Stenosis 605
By JAMES J. PAMPUSH, M.D., and ROBERT A. BRUCE, M.D., Seattle, Washington.

The Effects of Intravenous Infusions of the Optical Isomers of Dibozane (McN-181;1,4-Bis [1,4-Benzodioxan-2-Ylmethyl] Piperazine), an Adrenergic Blocking Agent, Upon Hypertensive Subjects 614
By LOUIS B. KRAMER, M.D., ROBERT VAN HORNE, M.D., SAMUEL BELLET, M.D., and GEORGE B. KOELLE, PH.D., M.D., Philadelphia, Pennsylvania.

The Cardiac Output of Normal Subjects Determined by the Dye-injection Method at Rest and During Exercise 622
By HENRY J. KOWALSKI, M.D., WALTER H. ABELMANN, M.D., WILLIAM F. MCNEELY, M.D., N. ROBERT FRANK, M.D., and LAURENCE B. ELLIS, M.D., Boston, Massachusetts.

Long-term Intravenous Use of Arfonad in the Treatment of Pulmonary Edema 626
By LAMONT E. DANZIG, CAPT., MC, and ALPHONSE C. GOMEZ, 1ST LT., MC, Fort Sam Houston, Texas.

Stress and Gastric Secretion in Man. I. A Study of the Mechanisms Involved in Insulin Hypoglycemia 630
By HARRY SHAY, M.D., and DAVID C. H. SUN, M.D., M.Sc., Philadelphia, Pennsylvania.

Simultaneous Pressure Measurements in the Hepatic Venule and Portal Venous System in Man 643
By GEORGE E. WELCH, M.D., ROBERT EMMETT, M.D., CLAUDE C. CRAIGHEAD, M.D., GEORGE HOEFFLER, M.D., DONOVAN C. BROWNE, M.D., and IRVING ROSEN M.,D., New Orleans, Louisiana.

N-Hydroxyethylethylenediamine Triacetic Acid, Versenol, in the Treatment of Hemochromatosis 646
By MARVIN J. SEVEN, 1ST LT., MC, USAR, HARRY GOTTLIEB, M.D., HAROLD L. ISRAEL, M.D., JOHN G. REINHOLD, PH.D., and MARTIN RUBIN, PH.D., Philadelphia, Pennsylvania and Washington, D. C.

Lack of Fat Ingestion on Blood Coagulation 652
By PHIL R. MANNING, M.D., and ROY L. WALFORD, M.D., Chanute Air Force Base, Illinois.

Certain Observations on the Uptake of Base in Uremia and Acidosis Due to Advanced Renal Disease 656
By RICHARD A. NEUBAUER, M.D., Wilmington, Delaware.

Studies of Thyroid Function in Myotonia Dystrophica 668
By C. E. BENDA, M.D., C. J. MALETSKOS, PH.D., J. C. HUTCHINSON, M.D., and E. B. THOMAS, S.M., Cambridge, Massachusetts.

Congenital Absence of a Main Branch of the Pulmonary Artery 673
By J. E. FLYNN, M.D., LT. (MC) USNR, A. A. SIEBENS, M.D., LT. (MC) USNR, and S. F. WILLIAMS, M.D., CAPT. (MC) USN, St. Albans, New York.

(Contents continued on page 12)

and the older antacid tablets just won't disintegrate!

now TREVIDAL® tablets

break up in less than a minute, assuring rapid yet prolonged relief of hyperacidity.

EACH TREVIDAL TABLET CONTAINS:

Balance of ingredients avoids constipation, diarrhea, or alkalosis	Aluminum hydroxide gel, dried . . . 90 mg. Magnesium trisilicate . . . . . 150 mg. Magnesium carbonate . . . . . 60 mg. Calcium carbonate . . . . . 105 mg.
Unique vegetable mucin supplies protective coat to irritated stomach lining	Regonol*† . . . . . 100 mg.
Binder controls and extends antacid activity	Egraine* . . . . . 45 mg.

AVAILABLE IN BOXES OF 100 TABLETS, SPECIALLY STRIPPED FOR EASY CARRYING.

†Cyamopsis tetragonoloba gum
*Trade Marks

Organon INC. • ORANGE, N. J.

PROGRESS OF MEDICAL SCIENCE

Medicine
(January and July)—G. E. Burch and C. Thorpe Ray

Neurology and Psychiatry
(January and July)—F. G. Ebaugh and Frank R. Drake

Surgery
(February and August)
I. S. Ravdin and C. G. Johnston

Ophthalmology
(February and August)
W. L. Benedict and H. P. Wagener

Preventive Medicine and Epidemiology
(March and September)
J. E. Gordon and Theodore H. Ingalls

Pathology and Bacteriology
(March and September)
G. Lyman Duff and E. G. D. Murray

Dermatology and Syphilology
(April and October)
J. H. Stokes, H. Beerman and N. R. Ingraham, Jr.

Oto-Rhino-Laryngology
(April and October)—N. D. Fabricant and A. Harry Neffson

Radiology
(May and November)—David M. Gould and Robert D. Sloan

Therapeutics
(May and November)
H. Gold and McKeen Cattell

Pediatrics
(June and December)—I. J. Wolman and A. M. Bongiovanni

Gynecology and Obstetrics
(June and December)
C. Bachman and Franklin L. Payne

(*Contents continued on page 14*)

THESODATE

The ORIGINAL ENTERIC-COATED TABLET OF THEOBROMINE SODIUM ACETATE . . .

PROVEN Effective IN ANGINA PECTORIS AND CORONARY ARTERY DISEASE

CLINICALLY PROVEN

Carefully controlled objective studies in humans and very extensive clinical experience have definitely proven the value of Theobromine Sodium Acetate in treating Angina Pectoris and Coronary Artery Disease.

RECOMMENDED DOSAGE

7½ grains q.i.d. before meals and before retiring. A capsule upon arising if necessary.

SUPPLIED

In bottles of — 100 — 500 — 1000

TABLETS THESODATE

*(7½ gr.) 0.5 Gm. . . . . *(3¾ gr.) 0.25 Gm.

THESODATE WITH PHENOBARBITAL

*(7½ gr.)	0.5 Gm. with	(½ gr.)	30 mg.
(7½ gr.)	0.5 Gm. with	(¼ gr.)	15 mg.
*(3¾ gr.)	0.25 Gm. with	(¼ gr.)	15 mg.

THESODATE, POTASSIUM IODIDE AND PHENOBARBITAL

Theobromine Sodium Acetate	(5 gr.)	0.3 Gm.
Potassium Iodide	(2 gr.)	0.12 Gm.
Phenobarbital	(¼ gr.)	15 mg.

Capsules also available in forms marked with asterisk (*) above in bottles of 25 — 100.

For sample—just send your ℞ blank marked 12TH12

Brewer EST. 1852

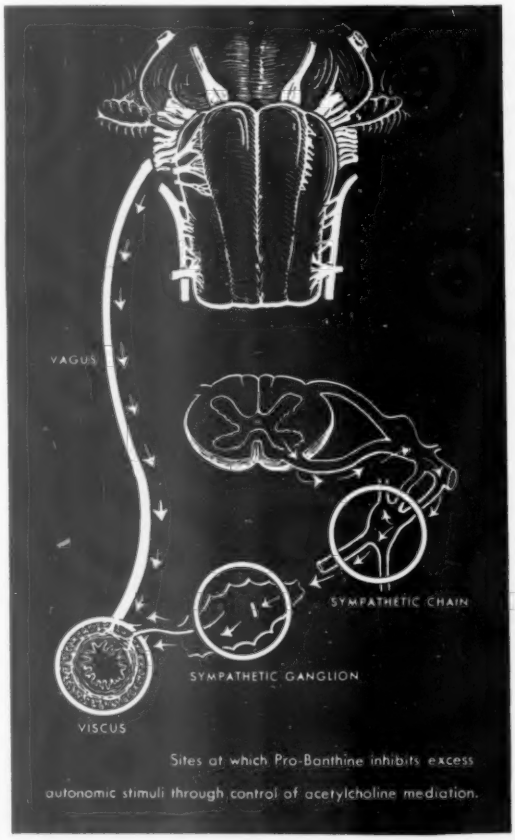
BREWER & COMPANY, INC.
WORCESTER, MASSACHUSETTS U. S. A.

Pro-Banthine®: For Anticholinergic Action in the Gastrointestinal Tract

Combined neuro-effector and ganglion inhibiting action of Pro-Banthine consistently controls gastrointestinal hypermotility and spasm and the attendant symptoms.

Pro-Banthine is an improved anticholinergic compound. Its unique pharmacologic properties are a decided advance in the control of the most common symptoms of smooth muscle spasm in all segments of the gastrointestinal tract.

By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas, regional enteritis and ulcerative colitis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.



Sites at which Pro-Banthine inhibits excess autonomic stimuli through control of acetylcholine mediation.

Roback and Beal[2] found that Pro-Banthine orally was an "inhibitor of spontaneous and histamine-stimulated gastric secretion" which "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon. . . ."

Therapy with Pro-Banthine is remarkably free from reactions associated with parasympathetic inhibition. Dryness of the mouth and blurred vision are much less common with Pro-Banthine than with other potent anticholinergic agents.

In Roback and Beal's[2] series "Side effects were almost entirely absent in single doses of 30 or 40 mg. . . ."

Pro-Banthine (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is available in three dosage forms: sugar-coated tablets of 15 mg.; sugar-coated tablets of 15 mg. of Pro-Banthine with 15 mg. of phenobarbital, for use when anxiety and tension are complicating factors; ampuls of 30 mg., for more rapid effects and in instances when oral medication is impractical or impossible.

For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

---

1. Schwartz I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

JMB 7164—B—7-30-54

CONTENTS (*Continued*)

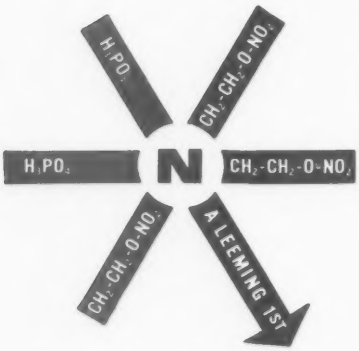
PEDIATRICS

Genetics in Pediatric Disease 680
By BARTON CHILDS, M.D., Baltimore, Maryland.

GYNECOLOGY AND OBSTETRICS

Carcinoma of the Endometrium 701
By ALFRED I. SHERMAN, M.D., and A. N. ARNESON, M.D., St. Louis, Missouri.

Angina pectoris prevention



The new strategy in angina pectoris is prevention, the new low-dose, long-acting drug—METAMINE. Most effective milligram for milligram, and better tolerated, METAMINE prevents attacks or greatly diminishes their number and severity. *Dosage:* 1 tablet (2 mg.) after each meal; 1-2 tablets at bedtime.

Thos. Leeming & Co. Inc.
155 EAST 44TH STREET, NEW YORK 17, N.Y.

Metamine®

Triethanolamine trinitrate biphosphate, Leeming, tablets 2 mg.
Bottles of 50 and 500.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

DECEMBER, 1954

ORIGINAL ARTICLES

NATURAL HISTORY, FUNCTIONAL CAPACITY AND EXERCISE TOLERANCE OF UNOPERATED PATIENTS WITH MITRAL STENOSIS*

I. Preliminary Results of One Year Follow-up

By James J. Pampush, M.D.
TRAINEE IN CARDIOLOGY, 1952-1953

AND

Robert A. Bruce, M.D.
ASSOCIATE PROFESSOR OF MEDICINE (CARDIOLOGY)

(From the Department of Medicine, University of Washington, Seattle, Washington)

It is generally recognized that mitral commissurotomy may yield impressive results in properly selected patients[1,2,8,11,13]. Yet with the nascent enthusiasm for surgical treatment it was easy to overlook some of the many facets of the natural history of mitral stenosis as it was presented to physicians.

Bland, Jones, and White followed 1000 children with rheumatic heart disease for 10 years and observed the disappearance of mitral systolic and diastolic murmurs in 53 of these children[3]. Grant observed that one-third of young adults with mitral stenosis died of heart disease within 10 years[10]. One-half of the survivors showed no progression of the disease, and were considered, for this reason, and because of absence of cardiac enlargement, to have a "good" prognosis. Soloff and Zatuchni found that precipitating factors were often responsible for the symptoms and manifestations of cardiac insufficiency in patients with rheumatic heart disease[14]. With appropriate medical treatment, the cardiac status often improved considerably for a prolonged period of time. Finally, many patients with mitral stenosis live for long periods before the lesion is even recognized. In 31 of 101 patients observed at necropsy by Graham and associates, the diagnosis of mitral stenosis was not made during life[9]. Although 47 of these 101 patients had marked mitral

*These studies have been supported in part by Grant-in-Aid H-908 (C) from the National Heart Institute of the National Institutes of Health.

TABLE 1.—CLINICAL CHARACTERISTICS OF PATIENTS (AT TIME OF INITIAL SURVEY)

			Age in Years of Recognition or Occurrence									
Patient	*Age*	*Sex*	*Acute Rheumatic Fever*	*Recurrence of ARF*	*Murmurs*	*Rheum. Heart Disease Diagnosis Made*	*Disability*	*Atrial Fibrillation*	*Arterial Emboli*	*Congestive Failure*	*Clinical Class*	*Reasons not Submitted to Surgery**
R. B.	38	F	7	Multiple	10	33	10	28	—	35	IV-D	1
F. S.	35	F	14	14	22	22	22 (Preg.)	30	35	34	IV-E	1
R. M.	40	M	23	—	19	39	36	—	—	39	IV-D	1
L. McL.	47	F	10	11 Multiple	13	13	33	Paroxysmal	—	45	II-B	2
H. R.	26	M	—	—	26	26	24	24	24	—	I-B	2
V. S.	25	F	—	—	19	19	19	—	—	22 (Preg.)	III-C	2
M. S.	47	F	31	—	44	44	44	—	—	—	II-C	2, 3
F. D.	56	M	—	—	55	55	46	56	—	—	III-C	2, 5
L. L.	50	F	9	—	29	36	35	—	—	50	II-C	2
A. L.	42	F	22	24, 26	22	40	40	—	—	29 (Preg.)	II-B	2
G. S.	33	M	—	—	25	26	26	—	—	—	III-C	3
V. M.	33	F	10	11, 29	7	15	29	—	—	29	III-C	3
E. R.	51	F	—	—	49	49	50	50	—	50	III-D	4
E. B.	40	F	—	—	39	39	36	—	—	37	III-D	4
F. C.	46	M	—	—	32	32	42	42	—	0	II-C	4
Range	25–56	10 F 5 M	7–31		7–55	13–55	10–50	24–56		22–50	I-IV	
Mean	40.6		16		27	33	33	38		37	2.7	

ARF = Acute Rheumatic Fever
RHD = Rheumatic Heart Disease
AF = Atrial Fibrillation
Preg. = Occurring during pregnancy

* 1 = Insufficient cardiac reserve to withstand surgery
2 = Insufficient need for surgery by our criteria
3 = Complicating lesions possibly contraindicating surgery
4 = Suitable indications, but surgery refused by patient
5 = Insufficient need with disability due largely to pulmonary disease (emphysema)

stenosis, the clinical records at the Boston City Hospital indicated that 15 of these patients had little or no cardiac disability prior to the terminal illness. Thirty-eight of these patients lived over 60 years and 13 lived over 70 years.

Physicians continue to encounter occasional patients who have mitral stenosis and get along surprisingly well with only minor disability. Contrariwise, not all patients submitted to commissurotomy maintain significant improvement. A recent study indicated that one-half of the patients operated had a delayed improvement with prolonged convalescence, and one-third showed heart failure in succeeding months[6]. Hence it is important to evaluate more closely the course of patients with mitral stenosis who are not submitted to mitral commissurotomy. This report presents data on such patients who were observed for one year.

Material and Methods. Fifteen patients were selected from a large group of patients evaluated for mitral commissurotomy on the basis that they were *not* submitted to surgery. The salient clinical characteristics of these patients are summarized in Table 1. There were 10 women and 5 men with an average age of 40.6 years. Although there was individual variation in the onset of symptoms and disease, the *average* age of occurrence of acute rheumatic fever was 16 years. Heart murmurs, symptoms of disability and heart failure were recognized at the mean ages of 27, 33 and 37 years, respectively. The functional capacity (classified according to the criteria of the New York Heart Association on a scale of I to IV)[12] averaged 2.7. Thus these patients were considered to be a representative sample of the group of patients with appropriate indications for mitral commissurotomy because mitral stenosis was the predominant valvular lesion responsible for cardiac symptoms.

These 15 patients were not submitted to mitral commissurotomy for the reasons stated in Table 1. The principles upon which these first 3 reasons were formulated have been described elsewhere[7]. Approximately one year later the patients were re-evaluated by the same observers in identical manner. Three class IV patients, ranging in age from 35 to 40 years, had died as a result of congestive heart failure (R.M. and R.B.), or pulmonary embolism (F.S.) in the intervening time. The data obtained from the remaining 12 patients form the basis of this report.

The methods of evaluation included a clinical history, physical examination, chest fluoroscopy and radiography, electrocardiograms and ancillary laboratory tests. All patients were studied by means of standardized exercise tolerance tests, as described previously[4,6*]. Statistical data were evaluated by means of Student's t test.

Results. A. CLINICAL OBSERVATIONS. The changes in the clinical findings in the 12 surviving patients evaluated again about one year after the initial appraisal are shown in Table 2. No symptom disappeared completely, but the incidence of orthopnea, paroxysmal nocturnal dyspnea, cough on exertion and hemoptysis diminished. Only one instead of 6 patients still had some evidence of congestive heart failure, and none showed signs of dependent edema. The number of patients requiring salt restriction and diuretics for control of cardiac edema was reduced. Since there was no increase in the number of patients taking digitalis, or requiring daily rest periods, it is suggested that the reduction in incidence of manifestations of pulmonary engorgement and congestion was probably due to the removal of unrecognized precipitating factors,

*The test consists of a walk on a treadmill ergometer operating at a rate of 1.7 M.P.H. on a slope representing a 10% grade. Recorded observations are made at one-minute intervals of of the blood pressure, heart rate, respiratory rate, respiratory efficiency (difference between oxygen concentration of inspired and expired air) and an apical precordial lead electrocardiogram. The test is initiated by 4 minutes of observations while the patient is sitting at rest, 1 minute of standing, 10 minutes of walking (unless symptoms necessitate cessation sooner) and 5 minutes of a recovery period in the sitting position. Minutes of endurance, respiratory efficiency and heart rate are integrated into a score called the Physical Fitness Index (PFI). In addition, changes in symptoms, signs, and electrocardiogram are noted during exercise.

such as respiratory infections, or excessive emotional or physical stresses.

The incidence of cardiac enlargement did not increase during the period of these observations. Possibly further valvular disease developed, with reference to the diastolic murmurs of mitral stenosis. On the average, however, the changes in murmurs were subtle, and probably within the range of individual variation in patients and observers alike (Table 3).

TABLE 2.—COMPARISON OF THE DISTRIBUTION OF CLINICAL FINDINGS IN 12 PATIENTS

Frequency of:	*Initially*	*One Year Later*
1. *Symptoms*		
Fatigue	11	10
Dyspnea on Exertion	11	11
Dyspnea at Rest	5	4
Orthopnea	6	1
Parox. Noct. Dyspnea	4	1
Chest Pain	7	6
Cough on Exertion	10	6
Hemoptysis	6	2
2. *Changes in Physical Activity*		
Limited	7	4
Required Daily Rest Periods	5	4
3. *Complications of R.H.D.* (History)		
Subacute Bacterial Endocarditis	1	0
Active Carditis	1	2
Arterial Emboli	2	0
Congestive Heart Failure	6	1
4. *Signs*		
Moderate Cardiac Enlargement	7	6
Atrial Fibrillation	5	5
Aortic Stenosis	5	6
Aortic Insufficiency	1	3
Mitral Insufficiency	8	8
Systolic Murmur along LSB	3	4
Pulmonary Congestion	5	3
Hepatomegaly	2	3
Dependent Edema	2	0
5. *Treatment*		
Daily Rest Periods	5	3
Digitalis	8	8
Salt Restriction	3	1
Diuretics	2	0
Adequately Treated	7	10
6. *Clinical Classification*		
I	2	0
II	5	8
III	5	4

especially in relation to the aortic valve (Table 2), but the changes in intensity of these murmurs was hardly significant, with the exception of patients L.L., G.S. and E.R.* There were variable changes in the murmurs arising from the mitral valve, more particularly

The changes in the functional classification also were variable, with more patients in class II on the second examination than initially.

B. EXERCISE TOLERANCE. The changes in the symptoms and signs observed during the same standardized stress of

*The early diastolic murmur in this patient was attributed to pulmonic insufficiency; actually it may have been associated with an early aortic lesion.

TABLE 3.—INTENSITY OF HEART MURMURS (GRADED I–VI) AND CLINICAL CLASSIFICATION (I–IV) INITIALLY AND AFTER AVERAGE INTERVAL OF ONE YEAR

Patient	*E.B.*	*F.C.*	*F.D.*	*L.L.*	*A.L.*	*H.R.*	*V.M.*	*L.Mc.*	*E.R.*	*V.S.*	*M.S.*	*G.S.*	*Mean*
Mitral Systolic	0*	II	I	0	II	II	III	0	II	0	III	II	2.1
	0	II	0	0	III	II	III	I	III	0	III	II	2.5
Mitral Diastolic	II	V	III	II	I	V	III	V	III	III	I	III	3.0
	III	III	III	II	IV	V	III	III	IV	IV	II	II	3.2
Aortic Systolic	0	0	0	0	I	0	0	I	0	0	I	III	1.6
	0	0	0	I	II	0	I	0	0	0	II	II	1.7
Aortic Diastolic	0	0	0	0	0	0	0	II	0	0	0	0	2.0
	0	0	0	II	0	0	0	III	0	0	0	III	2.6
Pulmonic Diastolic	0	0	0	II	0	II	I	III	0	II	0	0	2.0
	0	I	0	III	0	II	0	0	III	III	0	0	2.4
Tricuspid Systolic	0	0	0	0	0	III	II	0	0	0	0	II	2.3
	I	0	0	0	0	III	III	0	0	0	0	II	2.6
Clinical and Therapeutic Classification	III-D	II-C	II-B	II-C	I-B	I-C	III-D	II-B	III-C	III-C	II-B	III-C	2.3
	II-C	II-C	III-C	II-B	II-B	II-B	III-C	II-C	III-C	II-C	II-C	III-C	2.3

* In each block the upper figure is the initial evaluation; the lower figure the final evaluation.

exercise reflected the slightly improved status of the patients that was noted by clinical examination. For example, there was a very slight and statistically insignificant reduction in the average intensity of dyspnea with this particular exertion and similar change in the average intensity of fatigue (Table 4). Nevertheless, endurance increased from a mean of 7.6 to 8.6 minutes. The greatest change was an increase in the mean physical fitness index for this test from 9.3 to 12.0. This change approached, but did not actually achieve significance in a statistical sense (P .01 to .02). The factors responsible for this slight improvement were the endurance and the increased respiratory efficiency (from 3.8 to 4.3 volumes %), but the considerable individual variation precluded these changes being significant (P .02 to .05). It suggested, however, that the apparently improved rate of oxygen absorption by the lungs reflected an improved status in pulmonary function. Presumably this correlated with the clinical findings of diminished incidence of pulmonary engorgement and congestion.

In addition to these minor changes of borderline significance towards more nearly normal pulmonary function, there were slight variations in the mean systolic blood pressure. Thus the average pressure was lower during rest, and higher during the standardized exertion. Consequently the pulse pressure during exercise increased, and therefore approached the normal response. These changes were not significant statistically because of the range of individual variation.

Discussion. Ideally a control group should be limited to alternate patients who had proper indications for, but arbitrarily were not submitted to surgery. Since this was obviously not the case for every patient in this small series, some bias may have been introduced. Actually the 3 patients who refused surgery did not exhibit substantially different courses from other surviving patients who were not submitted to surgery for reasons indicated. Since none of the patients originally found to be in class IV were still alive, no further evaluation was possible for these individuals. It was of interest to observe, however, that those patients who died within months from their rheumatic heart disease ranged in age from 35 to 40 years. Thus their life expectancy was markedly reduced.

All of the patients originally considered to be in class I, II or III were still living about one year later. There was no substantial change in the manifestations of valvular heart disease in most patients. The most impressive clinical changes observed in these patients were the reduction in the incidence of symptoms, signs and treatment of pulmonary congestion and cardiac edema. Presumably this represented recovery from unrecognized precipitating factors that may have been responsible for the manifestations of cardiac insufficiency that prompted the patients to seek medical consultation initially. Since there was no increase in the number of patients receiving digitalis or observing daily rest periods, it was unlikely that these clinical changes could have been attributed to improved medical care. Seven of these 12 patients exhibited no change in the clinical classification of their functional capacity, and, although there were variations in the other 5 patients, there was no substantial change on the average.

There were no definitely significant changes (P less than .001) in any of the parameters routinely appraised by the standardized exercise tolerance tests in the 12 surviving patients. Nevertheless the endurance and respiratory efficiency during exercise increased in the follow-up tests one year later, and the

TABLE 4.—COMPARISON OF EXERCISE TOLERANCE*

	Initially								*Approximately One Year Later*							
	Dyspnea (Gr. 1–1+) During Standard Exercise	*Fatigue (Gr. 1–1+) During Standard Exercise*	*Endurance in Minutes of Standard Exercise*	*Resp. Eff. in Vol. % During Standard Ex.*	*Total Heart Rate of 3 Min. Recovery*	*Maximum Systolic B.P. During Rest*	*Maximum Systolic B.P. During Standard Ex.*	*Physical Fitness Index*	*Clinical Classification*	*Dyspnea (Gr. 1–1+) During Standard Exercise*	*Fatigue (Gr. 1–1+) During Standard Exercise*	*Endurance in Minutes of Standard Exercise*	*Resp. Eff. in Vol. % During Standard Ex.*	*Total Heart Rate of 3 Min. of Recovery*	*Maximum Systolic B.P. During Rest*	*Maximum Systolic B.P. During Standard Ex.*	*Physical Fitness Index*	*Clinical Classification*
R. B.	4	0	.8	2.1	380	154	154	.5	IV-D	Expired during the follow-up period								
F. S.	4	2	2.8	2.5	430	122	120	1.7	IV-E									
R. M.	3	0	1.3	1.9	244	152	152	1.0	IV-D									
L. McL.	1	2	10	4.2	390	129	142	10.7	II-B	0	1	10	5.1	373	125	148	13.7	II-C
H. R.	0	0	10	3.4	415	132	117	8.2	I-B	0	0	10	4.5	335	116	123	13.4	II-B
V. S.	2	3	10	4.9	389	116	120	12.6	III-C	0	0	10	4.1	310	97	118	13.2	II-C
M. S.	0	1	10	4.2	230	136	160	18.2	II-C	2	2	10	4.7	235	136	170	19.9	II-B
F. D.	4	0	1.3	2.6	320	120	80	1.0	III-C	4	0	2.3	4.4	308	120	120	2.3	III-C
L. L.	0	1	10	3.8	398	128	128	9.5	II-C	0	1	10	4.3	362	134	154	11.1	II-B
A. L.	1	1	10	4.6	281	110	135	16.4	II-B	2	0	10	4.2	243	120	126	17.3	II-B
G. S.	4	3	7	3.0	342	126	130	6.1	III-C	2	3	7.8	4.1	336	112	152	7.9	III-C
V. M.	4	0	2.5	3.9	237	104	98	4.1	III-C	3	0	10	4.2	265	90	110	15.8	III-C
E. R.	4	2	1.5	3.2	361	142	140	1.3	III-D	2	3	2.8	4.0	392	120	110	2.7	III-C
E. B.	3	1	10	3.8	429	118	135	8.8	III-D	2	0	10	3.8	428	117	122	8.9	II-C
F. C.	2	2	10	4.4	297	132	115	14.8	II-C	2	2	10	4.3	245	117	119	17.6	II-C
Range*	0–4	0–4	1.3–	2.6–	230–	104–	80–	1.0–	I–III	0–4	0–3	2.3–	3.8–	235–	90–	110–	2.3–	II–III
			10	4.9	429	142	160	18.2				10	5.1	428	136	170	19.9	
Mean	2.0	1.3	7.6	3.8	340	124	125	9.3	2.4	1.6	1.0	8.6	4.3	319	117	131	12.0	2.3
Mean Difference										−0.4	−0.3	+1.0	+0.5	−21	−7	+6	+2.7	−0.1
P												> .05	.02–.05	> .05		> .05	.01–.02	

* Not including first 3 patients who expired

greatest increment was in the physical fitness index from a mean of 9.3 to 12.0 which approached borderline significance. In addition there was slight although practically negligible improvement in the systolic and pulse pressures during exercise. It is suggested, therefore, that these changes paralleled the clinical observations of a decrease in the incidence of symptoms and signs as well as treatment of pulmonary congestion and cardiac edema. Hence these observations were in accord with those of Graham and associates that secondary pulmonary vascular changes played a role in the symptomatology of mitral stenosis, though there was no correlation between the severity of valvular stenosis and degree of increase of pulmonary vascular resistance[9].

It is apparent from these observations that any satisfactory appraisal of the functional capacity of patients after mitral valve surgery must take into account 2 important factors: First, none of the improvement attributed to surgery could be accounted for by preoperative medical treatment, particularly with respect to the precipitating factors that may have been responsible for the appearance of cardiac insufficiency. Thus the functional capacity needs to be re-evaluated preoperatively after a period of intensive medical treatment over a sufficiently long period of time. The exact details of each of these requirements of treatment and time can only be defined on terms of the particular clinical findings in each patient. Secondly the measurements of functional capacity a year or so after surgery should demonstrate statistically significant improvement, particularly with respect to exercise tolerance. This latter point is essential, inasmuch as the apparent increase in the physical fitness index of these unoperated patients approached borderline significance. Both of these requirements have been evaluated in patients selected by our criteria and tested by means of the standardizd exercise tolerance test[5,6].

Summary and Conclusions. 1. The clinical characteristics and tolerance of standardized exercise have been presented for 15 patients with rheumatic heart disease and mitral stenosis who were not submitted to mitral valve surgery for a variety of reasons.

2. When the patients were re-evaluated one year later, it was discovered that the 3 patients with class IV functional capacity had died of their disease or complications, despite the fact that their ages ranged from only 35 to 40 years.

3. There were no marked changes in the clinical manifestations of valvular heart disease in the 12 surviving patients with class I, II or III functional capacity.

4. There was a reduction in incidence of symptoms and signs, as well as treatment, of pulmonary congestion and cardiac edema in these 12 patients. These changes were attributed to recovery from the adverse effects of unrecognized precipitating factors, such as respiratory infection or excessive physical and psychological stresses, rather than to any increase in the number of patients receiving medical treatment.

5. The exercise tolerance of the 12 surviving patients exhibited an improvement of only borderline rather than definite significance with respect to the physical fitness index, endurance and respiratory efficiency. These changes reflected improved pulmonary function and were in accord with the clinical observation of a reduction in the manifestations of pulmonary engorgement.

6. It is concluded that patients should not be submitted to surgery unless there is evidence of persistent

symptomatology and disability, due to pulmonary engorgement secondary to mitral stenosis despite sufficiently prolonged medical treatment.

7. The standardized exercise tolerance test supplements the clinical appraisal of functional capacity. Serial tests may aid in the determination of the optimal time for surgical intervention.

REFERENCES

1. **Andrus, E. C., Blalock, A.,** and **Milnor, W. R.:** Arch. Surg., **67,** 790, 1953.
2. **Bailey, C. P., Bolton, C. P.,** and **Redondo Ramirez, H.:** Surg. Clin. N. America, **32,** 1807, 1952.
3. **Bland, E. F., Jones, T. D.,** and **White, P. D.:** J. Am. Med. Assn., **107,** 569, 1936.
4. **Bruce, R. A., Lovejoy, F. W., Yu, P. N. G.,** and **McDowell, M. E.:** Arch. Indust. Hyg., **4,** 236, 1951.
5. **Bruce, R. A., Merindino, K. A., Pampush, J. J.,** and **Sherson, E.:** Surgery, **36,** 621, 1954.
6. **Bruce, R. A.,** and **Rodgers, D. L.:** Am. J. Med., **1,** 35, 1953.
7. **Bruce, R. A., Rodgers, D. L.,** and **Merindino, K. A.:** Northwest Med., **52,** 201, 1953.
8. **Glover, R. P., O'Neill, T. J. E., Harris, J. S. C.,** and **Janton, O. H.:** J. Thoracic Surg., **25,** 55, 1953.
9. **Graham, G. K., Taylor, J. A., Ellis, L. B., Greenberg, D. J.,** and **Robbins, S. L.:** Arch. Int. Med., **88,** 532, 1951.
10. **Grant, R. T.:** Heart, **16,** 275, 1933.
11. **Harken, D. E., Dexter, L., Ellis, L. B., Farrand, R. E.,** and **Dickson, J. F.:** Ann. Surg., **4,** 722, 1951.
12. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. New York: New York Heart Association, 1953.
13. **Sellors, T. H., Bedford, D. E.,** and **Somerville, W.:** Brit. Med. J., **2,** 1059, 1953.
14. **Soloff, L. A.,** and **Zatuchni, J.:** J. Am. Med. Assn., **154,** 673, 1954.

THE EFFECTS OF INTRAVENOUS INFUSIONS OF THE OPTICAL ISOMERS OF DIBOZANE (McN-181;1,4-BIS[1,4-BENZODIOXAN-2-YLMETHYL]PIPERAZINE), AN ADRENERGIC BLOCKING AGENT, UPON HYPERTENSIVE SUBJECTS*

By Louis B. Kramer, M.D.†
RESIDENT IN CARDIOLOGY, PHILADELPHIA GENERAL HOSPITAL

Robert Van Horne, M.D.‡
RESIDENT IN CARDIOLOGY, PHILADELPHIA GENERAL HOSPITAL

Samuel Bellet, M.D.
PROFESSOR OF CLINICAL CARDIOLOGY
GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA
CARDIOLOGIST, PHILADELPHIA GENERAL HOSPITAL, AND GRADUATE HOSPITAL

AND

George B. Koelle, Ph.D., M.D.
PROFESSOR OF PHARMACOLOGY
DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY, GRADUATE SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA

(From the Division of Cardiology, Philadelphia General Hospital, and the Departments of Internal Medicine [Cardiology] and of Physiology and Pharmacology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania)

The effects on the blood pressure of hypertensive subjects produced by intravenous infusions of a new adrenergic blocking agent, Dibozane (McN-181; 1,4-bis[1,4-benzodioxan-2-ylmethyl]piperazine) were described recently by Rosenblatt *et al.*[10]. Although prior laboratory studies had demonstrated the compound to be an extremely potent hypotensive drug of low toxicity[9], moderate falls in pressure occurred during fewer than half the infusions into patients[10]. Furthermore, side effects were rarely severe but their incidence was high; those which occurred most frequently were drowsiness, weakness and tachycardia; dizziness, palpitation, slurred speech, dyspnea, apprehension and miscellaneous symptoms were noted occasionally. Electrocardiographic recordings of Wolff-Parkinson-White complexes were obtained in one patient. There were additional indications that, in the doses employed, the drug exerted direct effects on the cardiovascular system unrelated to adrenergic blockade, some of which might have opposed the hypotensive effect of the primary mechanism of action. Similar results were obtained in a clinical trial of Dibozane, administered orally, for the treatment of hypertension in ambulatory patients[6]. Some of the group who received the drug for several days or weeks obtained moderate falls in pressure, but nearly all experienced some of the aforementioned side effects.

*Preparations of the optical isomers of Dibozane (McN-181) were supplied by McNeil Laboratories, Inc., Philadelphia, Pennsylvania.

†Present address: Ohio State University Health Center, Columbus, Ohio.
‡Present address: 521 Cedar Avenue, Niagara Falls, New York.

Subsequent work has shown that the original preparation of Dibozane consists of approximately one-half meso-isomer and one-quarter each of the dextro- and levo-rotatory isomers (hereafter referred to as the meso, levo and dextro isomers)[11]. Following the resolution of the mixture, preparations of the individual isomers were made available for study. Observations of mice injected intraperitoneally with the 3 different isomers of Dibozane indicated that they might have distinct pharmacological actions while possessing the same order of toxicity (LD50 approximately 250 mg. per kg., intraperitoneally). In α-chloralose-anesthetized dogs, the levo isomer was the most potent in producing a lowering of blood pressure, reversal of the pressor effect of epinephrine and blockade of that of norepinephrine; it was twice as active in these respects as the original preparation. The meso compound was found to be approximately equipotent to the latter, and the dextro isomer about one-eighth as active[7]. In an earlier study of the pharmacological actions of the optical isomers of another adrenergic blocking agent, 883F, Bovet and Simon[1] found the levo isomer to be several times as potent as the dextro isomer in various species.

It was the purpose of the present investigation to compare the hypotensive activities and individual side effects of the 3 isomers of Dibozane in patients. If one should be found to be active in reducing blood pressure while producing a minimum of undesirable symptoms, it would obviously be potentially a more useful drug. Infusions of the dextro isomer were given 9 times, and of the levo and meso isomers 10 times each to a total of 10 hypertensive patients. Two of the group had received the unresolved preparation in the earlier study.

Methods. All patients selected had well-documented elevations of blood pressure, blood urea nitrogen values of 6 to 30 and negative phentolamine or piperoxan tests; their responses to sodium amytal were variable. Patients with a history of myocardial infarction were excluded. All patients showed cardiomegaly by roentgenograms and had electrocardiographic patterns indicating left ventricular hypertrophy or myocardial abnormality, or both. Although all appeared to have normal renal function on the basis of phenolsulfonphthalein and urine concentration tests, 3 had had nephrectomy: patient 4 for a renal calculus and patients 1 and 5 for undetermined reasons. Patient 4 had also undergone thoracolumbar sympathectomy approximately one year previously.

Sedation was withheld the night prior to each study, which was conducted in a quiet room. Patients remained supine and were made as comfortable as possible throughout the procedure. The infusion tubing was so arranged that solutions could be changed without the patient's knowledge. Auscultatory blood pressure readings and pulse rates were recorded every few minutes, and electrocardiographic tracings, usually of lead 1, were taken every 5 to 10 minutes. Initially and during the various periods the patient was asked simple questions relating to general and personal information and was asked to perform simple arithmetic tests. Responses were noted and various statements of the patient were recorded. In addition, the patient was observed for restlessness, confusion, somnolence, retching and other side effects. Dilutions were prepared immediately prior to infusion by adding 10.0 cc. of a 1% solution of the isomer in 7% lactic acid to 90.0 cc. of 5% glucose solution. During the initial control period, the patient was given an infusion of 5% glucose solution until the blood pressure appeared to be stabilized. The infusion was then changed to one of the isomers and at the termination of its administration, infusion of the control glucose solution was started immediately. Blood pressure was allowed to stabilize again, after which another isomer was given. Two different isomers were infused in 4 tests, and all 3 isomers were given in sequence 7 times. The order in which the different isomers were given was varied in all possible combinations (Table 1).

Results. A. EFFECTS ON BLOOD PRESSURE AND HEART RATE. In order to provide a comparison of the relative hypo-

tensive activities of the 3 isomers, we have plotted all systolic and diastolic pressure readings obtained during the infusion and subsequent control periods. Accordingly, the exact changes during any given infusion can be read,

TABLE 1.—SEQUENCE OF ADMINISTRATION, DOSES, AND PERIODS OF INFUSION OF OPTICAL ISOMERS OF DIBOZANE (McN–181).

Patient	*Sequence of Isomers*	*Dose mg.*	*Period min.*
1	D	80	34
	L	86	35
2	D	91	35
	M	70	26
2A*	L	64	21
	M	95	35
3	L	56	35
	M	100	54
4	M	92	25
	L	97	31
	D	95	25
5	L	78	34
	D	86	22
	M	65	21
6	D	95	45
	M	68	17
	L	85	26
7	M	81	29
	D	96	30
	L	95	28
8	L	98	56
	M	92	34
	D	95	28
9	D	90	30
	L	42	17
	M	96	30
10	D	100	28
	M	100	28
	L	90	37
	L†	100	27

* Same patient as 2, infusion given one week later.

† Thirty-one minute interval between the two infusions of the L-isomer.

but a glance at each figure permits assessment of the general trend of pressures.

The dextro isomer was found to exert no significant effect on blood pressure or pulse rate in the 9 patients who received doses ranging from 80 to 100 mg. over periods of 22 to 45 minutes. The absence of any change is reflected in the relatively horizontal lines of Fig. 1.

The levo isomer was given in a dosage range of 42 mg. to 100 mg. in time intervals varying from 17 to 56 minutes. The lower dosages and shorter time periods were generally determined by marked responses of the patients. There were marked falls in pressure in 5 of the 10 subjects, the changes in minimum blood pressure values from the prior control periods to during or after the infusion periods being as follows: patient 1 (78/50), 2A (90/40), 3 (126/80), 8 (34/30) and 9 (76/14). These changes are indicated in Fig. 2 by the steep slopes of the plots. Patient 5 had no change in blood pressure but developed a sinus tachycardia; the pulse rate rose from 100 to 108 to 142 during the infusion of 78 mg. This patient had had amputation of both legs in his youth and a subsequent nephrectomy. He had exhibited the same rise in pulse with no fall in blood pressure when given the unresolved mixture in the previous study. Patient 4, who had undergone bilateral thoracolumbar sympathectomy, showed only a moderate decrease in blood pressure, namely, 22/12 with a dose of 97 mg. infused over 31 minutes. Prior to and during the infusion she manifested constant shivering. The significance of this result is further complicated by the fact that she developed a gradual fall following the preceding infusion of the meso isomer, and the pressure might not have become completely stabilized during the intervening control period. The latter situation may also account for the lack of hypotensive response to the levo isomer in patients 6 and 7, both of whom showed moderate falls during the prior infusion of the meso compound.

In the course of 10 infusions of the meso isomer over a dosage range of 65 to 100 mg. given in 17 to 54 min-

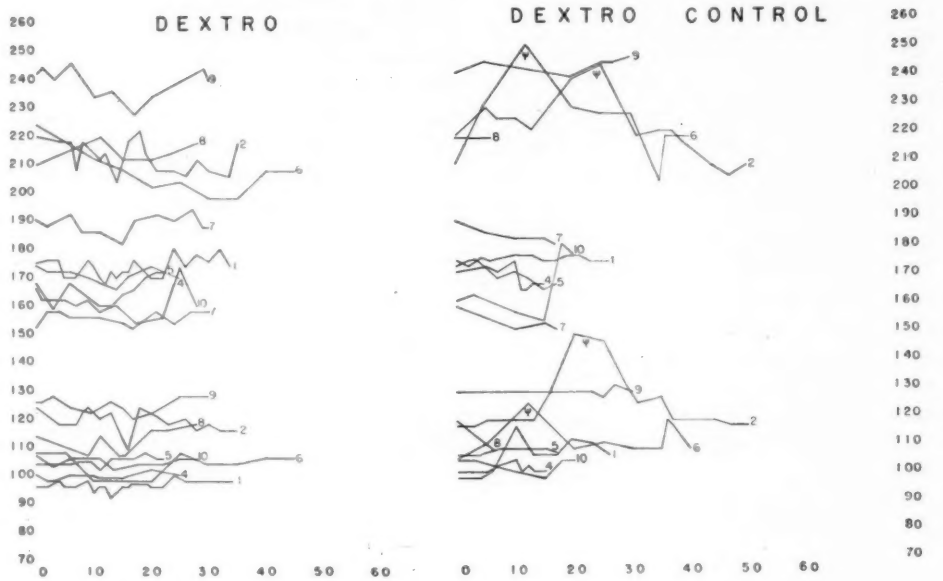


Fig. 1.—Systolic and diastolic pressures of 9 patients during infusions of the dextro isomer of Dibozane, and during the immediately subsequent control periords.

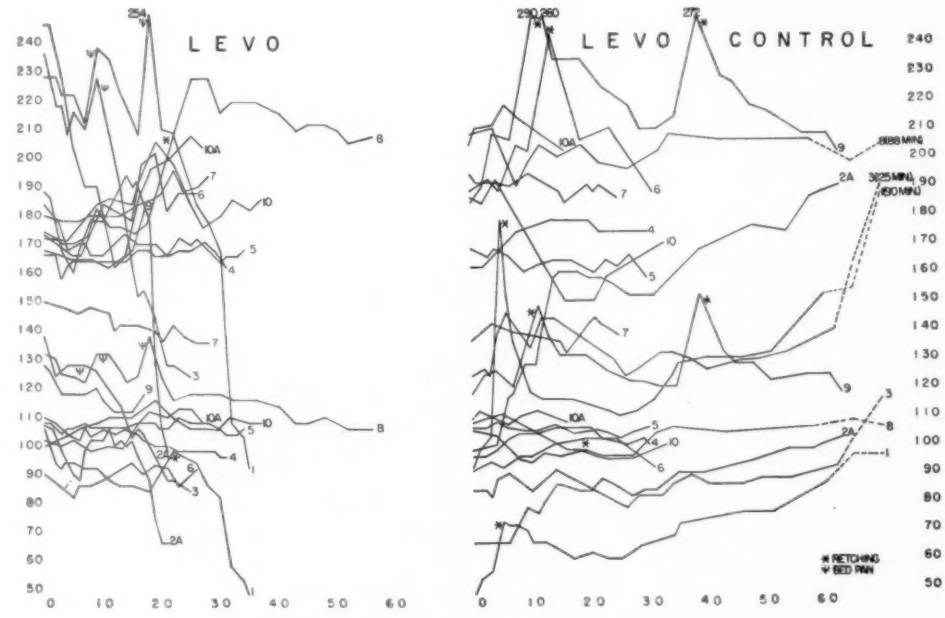


Fig. 2.—Systolic and diastolic pressures of 10 patients during infusions of the levo isomer of Dibozane, and during the immediately subsequent control periods.

utes, marked falls in blood pressure occurred 3 times, in patients 2 (40/30), 6 (54/40) and 7 (20/36) (Fig. 3). In 4 patients (2A, 3, 8 and 9) who had received infusions of the levo isomer prior to the meso compound, the former produced vasodepression but the latter did not. Patients 5 and 10 showed no hypotensive response to either the meso or levo isomer. Patients 2A and 9 exhibited moderate tachycardia and patient 6 had a slight rise in pulse rate, as with the levo compound.

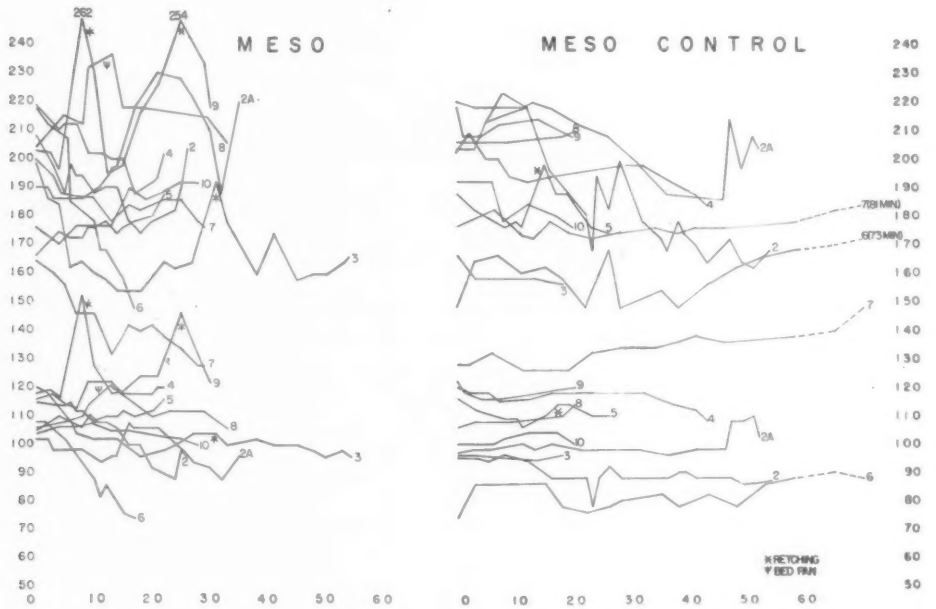


Fig. 3—Systolic and diastolic pressures of 10 patients during infusions of the meso isomer of Dibozane, and during the immediately subsequent control periods.

B. EFFECTS ON ELECTROCARDIOGRAM. No significant electrocardiographic changes occurred during or after infusions of the dextro isomer.

Five patients exhibited significant electrocardiographic changes with the levo isomer. Patient 2A developed premature beats with short bouts of nodal rhythm at the rate of 44 per minute, starting 7 minutes from the beginning of the infusion and persisting until 14 minutes after its discontinuation. At the same time, the T waves became more inverted. Patient 4 also developed auricular and nodal premature contractions, with bouts of nodal rhythm beginning 7 minutes after the start of the infusion. Sinus tachycardia was exhibited by patients 5 and 9; in both cases, the heart rate increased by approximately 40 beats per minute about 5 minutes from the beginning of infusion. A wandering pacemaker developed in patient 3, accompanied by episodes of nodal rhythm with retrograde conduction which persisted for 25 minutes after the cessation of the infusion. Minor changes in the T wave (increase in height, or increased inversion) were noted in most of the patients, but these were apparently of

little significance since equal or greater changes of the same types could be produced by changes in body position.

The meso isomer produced considerably less modification of the electrocardiographic pattern. During its infusion occasional auricular premature contractions were noted in patients 2 and 4. Slight lowering of the ST and T segments, accompanied by complaints of precordial distress, occurred in patient 6 approximately 10 minutes after the beginning of infusion. Sinus tachycardia (140) and increased inversion of the T wave occurred in patient 9 shortly after the infusion was terminated. The height of the T wave increased slightly in patient 3.

C. SIDE EFFECTS. The only symptom noted during or after infusions of the dextro isomer was slight drowsiness. Since this occurred with approximately equal frequency during control periods, it was due most likely to the prolonged period during which the patients remained supine.

Drowsiness occurred during 7 of the 10 infusions of the levo isomer; in 2 cases it was marked. Other side effects and their frequencies resulting from the levo isomer were nausea (6), restlessness (5), palpitation (4), desire to urinate or defecate (4), vomiting (3), complaints of difficulty in breathing (2), chills (2) and singultus (2). Single instances occurred of headache, slurred speech, and inability to answer questions. There was no evidence of disorientation, confusion or dizziness.

The most striking difference between the meso isomer and the other 2 was in the marked effects of the former on the higher cerebral centers. During 9 of the 10 infusions of the meso compound there was impairment in the patients' thinking and recall abilities which was marked in 8 cases, moderate in 1 and absent only in patient 6. These effects came on early during the infusions and cleared up completely from 5 minutes to half an hour after their termination, and were characterized by inability to answer routine questions or to do simple subtractions. Only patient 7 exhibited a similar response to the levo isomer, and with the latter it was much less pronounced. Other central effects of the meso compound and their frequencies were confusion (6), disorientation (4), restlessness (4), slurred speech (4) and dizziness (2). In patients 2 and 5, behavior bordered on a psychotic state and was accompanied by extreme restlessness and aggressiveness. Additional side effects with the same isomer were drowsiness (6), nausea (5), vomiting (3), headache (2), palpitation (2), urge to urinate or defecate (2), shivering (1) and singultus (1).

Discussion. The foregoing results indicate that the administration of the individual optical isomers of Dibozane permits dissociation of the undesirable effects from the hypotensive action only to a limited extent. The side effects of impaired cerebration, dizziness, slurred speech, confusion and disorientation were observed almost exclusively with the meso isomer. The development of nodal beats and rhythms and wandering pacemaker occurred only with the levo compound. On the other hand, both the levo and meso isomers produced drowsiness, palpitation, nausea, vomiting, restlessness and urinary and defecatory urgency. While both the levo and meso isomers were able to lower the blood pressure, the action of the former was more pronounced in this regard, both in the number of subjects affected and in the degree of lowering. We did not substantiate the previous impression[10] that failure of the blood pressure to respond was due to compensatory tachycardia. As examples, patient 10 had no change in blood pressure or in heart rate with

either the levo or meso isomer, whereas patient 9 showed a fall in pressure after the levo isomer although she developed tachycardia. The dextro isomer produced no significant hypotension or side effects in any of the patients.

It has been mentioned that the order in which the levo and meso isomers were administered seemed to be an important determining factor in some patients who responded with a fall in pressure after the first isomer given but were unresponsive to the second. Prior administration of the dextro isomer did not appear to influence the effect of either of the others. These impressions were supported by the results in the patient who received infusions on two separate occasions (2 and 2A). When the meso compound followed the dextro, a marked fall in blood pressure occurred. On the second occasion, when the levo isomer was given prior to the meso, the latter caused no significant change whereas the levo isomer had caused a marked temporary drop. In addition to the possible explanation given above, that insufficient time was allowed for the stabilization of pressure between infusions, the reciprocal influences of the levo and meso isomers might be explained on the basis of either mutual tachyphylaxis or mutual antagonism. Examples of both phenomena have been reported for optical isomers of sympathomimetic amines. Thus, Chen *et al.*[2] demonstrated mutual tachyphylaxis with the optical isomers of ephedrine, in that an initial injection of one resulted in a diminution of the expected pressor response to another given subsequently. Tainter and Seidenfeld[12] found that doses of the dextrorotatory isomer of synephrine which were inactive in the perfused rabbit's ear antagonized the vasoconstrictor effect of the levorotatory isomer. In addition to the vasodepressor effects of the isomers of Dibozane, one aspect of their side effects might be attributed to mutual antagonism. The outstanding cerebral symptoms produced by the meso isomer in the present study were not observed in the earlier study when the original preparation was employed, excepting in one patient who had a precipitous fall in blood pressure after receiving a high dose of the drug orally[10]. It is possible that this action of the meso isomer was prevented by the presence of the levo or dextro isomer in the unresolved preparation.

The therapeutic limitations of adrenergic blocking agents in general have been reviewed, and reasons presented for their inability to lower blood pressure without producing undesirable effects in a high percentage of patients[3,8]. The present results do not appear to modify this picture essentially, for doses of both the levo and meso isomers of Dibozane which produced significant vasodepression in hypertensive patients also caused well-defined side effects. However, the use of drugs of this type as adjuncts to other agents in the treatment of hypertension has not been explored sufficiently, and this aspect of their possible use deserves further study. At a lower dosage range, Dibozane might potentiate the hypotensive action of a drug acting by another mechanism without producing undesirable effects. In addition, the compound's pharmacological potency and relatively limited toxicity indicate that it may be of value in the therapy of various types of peripheral vascular disease, where results to date with adrenergic blocking agents have been encouraging[4,5].

Summary. 1. The individual optical isomers (dextrorotatory, levorotatory and meso) of Dibozane (McN-181) were given by intravenous infusion to 10 hypertensive patients in order to determine their relative vasodepressor

potencies and characteristic side effects. Two isomers were administered on 4 occasions and all 3 isomers on 7 occasions, with a control period following the infusion of each isomer.

2. The dextro isomer (80 to 100 mg. in 22 to 45 minutes) caused no significant hypotensive or side effects in 9 patients.

3. The levo isomer (42 to 100 mg. in 17 to 56 minutes) produced significant falls in blood pressure (34/30 to 126/80) in 5 of 10 patients. The most outstanding side effects were cardiac arrhythmias, including auricular and nodal premature contractions (2), sinus tachycardia (2) and wandering pacemaker (1). The other side effects which occurred most frequently were drowsiness (7), nausea (6), restlessness (5), urinary or defecatory urgency (4) and vomiting (3).

4. The meso isomer (65 to 100 mg. in 17 to 54 minutes) produced significant vasodepression (20/36 to 54/40) in 3 of 10 patients. Marked temporary impairment of thinking and recall abilities occurred 8 times, along with confusion (6), disorientation (4) restlessness (4) and slurred speech (4); other side effects were drowsiness (6), nausea (5) and vomiting (3).

5. Although the levo isomer was found to be the most potent vasodepressor agent in essential hypertension, its side effects limit its potential therapeutic usefulness. Possible applications of Dibozane as an adjunct in the treatment of hypertension and as a therapeutic agent in other conditions are discussed.

REFERENCES

1. **Bovet, D.**, and **Simon, A.**: Bull. Sci. Pharmacol., **42**, 466, 1935.
2. **Chen, K. K., Wu, C.-K.**, and **Henriksen, E.**: J. Pharmacol. & Exper. Therap., **36**, 363, 1929.
3. **Green, H. D.**: Am. J. Med., **17**, 70, 1954.
4. **Green, H. D., Gobel, K., Moore, M. J.**, and **Prince, T. C.**: Circulation, **6**, 520, 1952.
5. **Green, H. D.**, and **Grimsley, W. T.**: Ibid., **7**, 487, 1953.
6. **Gunn, C. G.**: Personal communication.
7. **Marsh, D. F.**: Personal communication.
8. **Nickerson, M.**: Am. J. Med., **8**, 342, 1950.
9. **O'Leary, J. F.**: Fed. Proc., **12**, 355, 1953.
10. **Rosenblatt, W. H., Haymond, T. A., Bellet, S.**, and **Koelle, G. B.**: Am. J. Med. Sci., **227**, 179, 1954.
11. **Swain, A. P.**: Personal communication.
12. **Tainter, M. L.**, and **Seidenfeld, M. A.**: J. Pharmacol. & Exper. Therap., **40**, 23, 1930.

THE CARDIAC OUTPUT OF NORMAL SUBJECTS DETERMINED BY THE DYE-INJECTION METHOD AT REST AND DURING EXERCISE*

By Henry J. Kowalski, M.D.
INSTRUCTOR, DIVISION OF CARDIOLOGY, UNIVERSITY OF WASHINGTON MEDICAL SCHOOL, SEATTLE; FORMERLY POST-DOCTORAL RESEARCH FELLOW, LIFE INSURANCE MEDICAL RESEARCH FUND

Walter H. Abelmann, M.D.
RESEARCH FELLOW OF THE AMERICAN HEART ASSOCIATION

William F. McNeely, M.D.
FORMERLY RESEARCH FELLOW, THORNDIKE MEMORIAL LABORATORY

N. Robert Frank, M.D.
FORMERLY RESEARCH FELLOW, THORNDIKE MEMORIAL LABORATORY

AND

Laurence B. Ellis, M.D.
ASSOCIATE CLINICAL PROFESSOR, HARVARD MEDICAL SCHOOL; ASSOCIATE PHYSICIAN, THORNDIKE MEMORIAL LABORATORY, BOSTON CITY HOSPITAL, AND DIRECTOR, CARDIAC CLINIC, BOSTON CITY HOSPITAL

(From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts)

Knowledge of the cardiac output is of fundamental importance in the description and understanding of hemodynamic phenomena. The Fick procedure has been widely and successfully used in determining cardiac output at rest. However objections may be raised to its use during exercise; and further, cardiac catheterization necessary for the Fick method, may be a formidable procedure for the seriously ill patient. Recent studies suggest that the indicator-dilution technique, also known as the injection-method, for determining cardiac output is of value during exercise and can be used in seriously ill patients[1-3, 5,7,8].

In this communication we report on the use of the injection-method in normal subjects during rest and exercise.

Methods. Twenty-four subjects were studied at rest, and 9 of these during rest and exercise. Four were house officers and the remainder were hospitalized patients without cardiovascular disease.

Observations were made in the early morning, in the post-absorptive state and in recumbency. No sedatives were administered.

Cardiac output was determined by means of the dye-injection method of Hamilton and co-workers[6] with minor modifications as reported previously[7]. Five milligrams of a 0.5% solution of Evans blue dye were injected rapidly through an indwelling venous needle from a tuberculin syringe previously calibrated by weighing. The dead space of the indwelling needle was known and accounted for in determining the

*Sponsored in part by the Massachusetts Heart Association.

amount of dye injected. Samples of arterial blood were collected by free-flow from an indwelling arterial needle through a short length of polyethylene tubing into heparinized tubes mounted along the rim of a circular lucite disc equipped with funnels arranged so that spillage between tubes was minimized. Flow through the polyethylene tubing was constant but pulsatile. The disc was rotated about a centrally placed vertical shaft by a variable-speed electric motor. The usual collection time for each tube was 2 to 2½ seconds. Samples of arterial blood were centrifuged for 20 minutes at 3,000 rpm and the concentration of dye in undiluted plasma was determined in micro-cells at a wave length of 625 millimicrons using a Beckman Model DU spectrophotometer. Oxygen consumption was measured in the subjects studied both at rest and exercise. An open circuit method was used, the expired air being collected in a Douglas bag over a period of 3 minutes. During the 2nd minute of collection the resting cardiac output was determined. The volume was measured in a Tissot spirometer. Oxygen concentration was determined by means of a Pauling oxygen analyzer. Carbon dioxide was not measured. The average respiratory quotient of Dexter and associates[4] was used for converting expired volume to inspired volume. Exercise was performed in recumbency and consisted of pedaling a bicycle ergometer at an approximate rate of 50 rpm. External work was not measured; the oxygen consumption served as an index of work performed. Simultaneous determinations of cardiac output and oxygen consumption were carried out between the tenth and fifteenth minutes of steady exercise.

Results. REST (Table 1). The mean value of cardiac index in the 24 subjects studied at rest was 3.60 ± 0.62 L./min./M^2. (Mean $\pm$ S.D.). This mean agrees very well with means obtained in normal subjects using a similar method by Chapman and Fraser[3] and by Smith, Wikler and Fox[8]. Both sets of data are also summarized in Table 1.

EXERCISE (Table 2). As might be expected the exercise resulted in increased oxygen consumption and cardiac output. The oxygen consumption during exercise ranged from 1.8 to 4.7 times control values and averaged about threefold.

The mean increase of blood flow was 505 cc. per 100 cc. increase in oxygen consumption with a standard deviation of $\pm$ 397 cc. One subject, H.I., tripled his oxygen consumption during exercise but only had a slight increase in cardiac output. This man had been a long distance runner in college.

Responses to exercise thus showed considerable variation.

It is noted that blood samples of adequate size for colorimetric analysis were uniformly obtained by the free-flow or gravity method, and suction devices were not employed.

Discussion. In a recent communication[7], we analyzed the data of 6 authors who reported cardiac output estimations in normal subjects determined by the Fick principle. Mean values of cardiac index (as calculated by us) in the various samples ranged from 3.27 to 3.79 L./min./M^2., and the standard deviations of the various samples were between $\pm$ 0.54 and $\pm$ 0.83. The estimates of cardiac index as reported here determined by the dilution-indicator method agree well with the above, but the means in Table 1 may be slightly higher. If so, the difference is not great.

Smith and his co-workers[8] have subjected data from studies where simultaneous Fick and dilution methods of determining cardiac output were employed to statistical analysis to deter-

mine if a systematic difference exists between the two methods. Their analysis indicated a significant difference between the two techniques in the largest series studied, (68 patients: Werkö and associates[9]); and, a systematic difference when the data from all the laboratories were combined. A similar analysis of the same material performed by one of us (HJK), using a technique wherein the mean differences of paired observations were examined to determine if they fell at random about zero, justified the same conclusion. Smith and associates[8] point out that although the difference between the two techniques is significant it is a small difference and the agreement between the two methods in different laboratories is good.

The response to exercise in the subjects studied here was variable. This was the general experience of Chapman and Fraser[3] who studied the cardiac output of normal subjects during exercise consisting of a 10-minute walk at a speed of 3 miles per hour and at a 5% grade, and employed the dilution-indicator methods. This level of exercise corresponds to an average oxygen uptake of 1214 cc./minute, and would be about a 4 to 5 fold increase over resting values. Cardiac index at exercise

TABLE 1.—CARDIAC INDEX DETERMINED BY THE DILUTION-INDICATOR METHOD IN "NORMAL" SUBJECTS

Author	*Material*	*Cardiac Index ± S.D. L./min./M²*
Chapman and Fraser[3]	23 Normal Men Age (18–39)	3.63 ± 0.59
Smith, Wikler and Fox[8]	2 Females 8 Males Patients without C.V. Disease Age (21–55)	3.51 ± 0.34*
Present Authors	23 Males 1 Female Normals and Patients without C.V. Disease Age (16–41)	3.60 ± 0.62

* Computed by us from authors' data.

TABLE 2.—CARDIAC OUTPUT DURING EXERCISE IN "NORMAL" SUBJECTS

		Rest			*Exercise*		
Subject	*Age*	*C.O. L/min.*	*C.I. L/min./M²*	*O_2 cons. cc./min. S.T.P.*	*C.O. L/min.*	*C.I. L/min./M²*	*O_2 cons. cc./min. S.T.P.*
H. I.	31	5.98	3.17	314	6.30	3.34	950
A. R.	27	7.83	3.63	298	10.35	4.79	996
W. I.	28	7.70	3.69	298	10.37	4.96	920
M. A.*	33	4.92	2.72	223	5.67	3.14	1043
S. A.	25	6.53	3.12	280	12.40	5.94	1220
J. W.	21	6.88	4.19	289	13.18	8.05	582
S. Z.	38	6.48	4.47	293	9.08	6.26	830
J. L.	42	4.46	2.75	210	11.30	7.02	700
B. A.	40	6.69	3.34	358	8.49	4.29	602

* Female. All others, males.

under this standard work load was 6.32 ± 1.37 (4.03 to 9.91) L./min./M^2. The response thus was quite variable in contrast to their experience at rest.

Dexter and associates[4] studied a group of healthy untrained individuals by means of the Fick method. The exercise performed was comparable to that done in the present study. The mean increment in blood flow per 100 cc. increase in oxygen consumption was 537 cc. $\pm$ 356 (Mean $\pm$ S.D., values computed by us). These results are in agreement with our data cited above.

From the above, it appears that the variation noted here is due, in part, to differences between individuals since the response to exercise of normal subjects covers a wide range.

In the studies reported here free arterial flow was employed to secure arterial samples, and suction was not used. In a large series of estimates of cardiac output in subjects with normal hematocrit, and those with anemia[2,7] difficulties in securing ample specimens for colorimetric analysis of dye concentration, were rarely encountered. However, studies of patients with polycythemia secondary to pulmonary disease have often been unsatisfactory in our hands since the increased blood viscosity apparently limited the arterial outflow during the collection period (unpublished observations). In such patients a suction method for collecting larger samples may be necessary.

Summary and Conclusions. The dye-injection method of estimating cardiac output yields reproducible results in subjects without cardiovascular disease when studied at rest. Agreement among different laboratories is good.

There is a small but significant difference between simultaneous estimates of cardiac output determined by the Fick and by the dye-injection method in normal subjects at rest. Use of the latter technique gives slightly higher values but the difference is not great.

The dye-injection method may be used utilizing free arterial outflow during exercise performed in recumbency. Such results show some variation due in part to the wide spectrum of hemodynamic responses displayed by normal subjects in exercise. Similar variation is noted with the Fick method.

It is concluded that the injection method of estimating cardiac output can be used at exercise as well as during rest.

ACKNOWLEDGMENT: We are grateful for the technical assistance of Miss Vilma Grube.

REFERENCES

1. **Abelmann, W. H., Kowalski, H. J.,** and **McNeely, W. F.:** Quart. J. Stud. Alcohol, **15,** 1, 1954.
2. Iidem: J. Clin. Invest., in press.
3. **Chapman, D. B.,** and **Fraser, R. S.:** Circulation, **9,** 57, 1954.
4. **Dexter, L., Whittenberger, J. L., Haynes, F. W., Goodale, W. T., Gorlin, R.,** and **Sawyer, C. G.:** J. Appl. Physiol., **3,** 439, 1951.
5. **Gilbert, R. P., Goldberg, M.,** and **Griffin, J.:** Circulation, **9,** 847 1954.
6. **Hamilton, W. F., Riley, R. L., Attyak, A. M., Cournand, A., Fowell, D. M., Himmelstein, A., Nobel, R. P., Remington, T. W., Richards, D. W., Jr., Wheeler, N. C.,** and **Witham, A. C.:** Am. J. Physiol., **153,** 309, 1948.
7. **Kowalski, H. J.,** and **Abelmann, W. H.:** J. Clin. Invest., **32,** 1025, 1953.
8. **Smith, W. W., Wikler, N. S.,** and **Fox, A. C.:** Circulation, **9,** 352, 1954.
9. **Werkö, L., Lagerlöf, H., Bucht, H., Wehle, B.,** and **Holmgren, A.:** Scandinav. J. Clin. & Lab. Invest., **1,** 109, 1949.

LONG-TERM INTRAVENOUS USE OF ARFONAD IN THE TREATMENT OF PULMONARY EDEMA

By Lamont E. Danzig, Capt., MC*

and

Alphonse C. Gomez, 1st Lt., MC

(From the Surgical Research Unit and Medical Service, Brooke Army Medical Center, Fort Sam Houston, Texas)

The ganglionic blocking action of a thiophanium compound, commercially known as Arfonad (RO 2-2222)†, was first described by Randall, Peterson, and Lehmann[3]. A physiologic similarity was noted in anesthetized animals between this compound and tetraethylammonium chloride. However, Arfonad effectively reduced blood pressure at much lower dosage levels than tetraethylammonium chloride. This more efficient reduction in blood pressure by Arfonad may depend, in part, upon direct peripheral vasodilation[1].

In a study on the neurohemodynamics of pulmonary edema, Sarnoff induced increased pulmonary venous pressure in animals and noted that Arfonad decreased the pressure; concomitantly, the mean systemic arterial pressure was decreased only slightly[7]. He also demonstrated that 1) the rate and degree of sympathetic blockade could be controlled with minimal side effects, and 2) that cessation of the intravenous drip containing this drug was followed by a prompt return of arterial pressure to control levels[2].

Sarnoff used Arfonad by continuous intravenous drip in several patients who had pulmonary edema associated with severe arterial hypertension and noted striking improvement in some cases[6]. The studies were carried out only for a few hours, but the absence of untoward reactions suggested the possible usefulness of this drug in the control of hypertension for longer periods of time[2]. However, the effectiveness and toxicity of, and tolerance to Arfonad following prolonged therapy have not been evaluated.

Recently a patient, who had chronic glomerulonephritis complicated by hypertension and severe pulmonary edema, was treated with Arfonad given intravenously for a total of 11 days. The blood pressure was lowered and the pulmonary edema cleared. Tolerance to the drug did not vary, and very few side effects were noted. This case is reported, since it represents the first extended trial of the continuous intravenous infusion of Arfonad.

Case Report. A 19-year-old white man was transferred from another military installation with a diagnosis of chronic glomerulonephritis. Three months prior to admission to Brooke Army Hospital, the patient began to have nausea, vomiting, and exertional dyspnea. He was admitted to a base hospital, and hypertension, uremia, and moderate anemia were noted. Treatment consisted of blood transfusions, intravenous fluids, sodium restriction, antibiotics, and bed rest. Rapid clinical deterioration prompted transfer to Brooke Army Hospital where more elaborate facilities are available.

*Present address: 603 East 59th Street, Savannah, Georgia.

†The authors wish to express their thanks to Dr. Thomas C. Fleming of Hoffmann-La Roche, Inc., Nutley, New Jersey, for generous supplies of the compound used in this study.

The past medical history revealed that albuminuria had been discovered 2 years before, and following a brief hospitalization, moderate restriction of physical activity was advised.

On admission to Brooke Army Hospital, the patient appeared moribund, though his sensorium was clear. The blood pressure was 170/100, the pulse rate 86, the respiratory rate 36, and the temperature 98.6° F. The patient was cyanotic and tremulous. Respiratory movements were entirely diaphragmatic, and there was a complete flaccid paralysis of all the extremities. Moderate sacral and ankle edema was present, and the neck veins were slightly distended. The fundi were normal except for minimal arteriolar spasm and arteriovenous nicking. Auscultation of the lungs revealed numerous rhonchi. There was left cardiac enlargement and a gallop rhythm. The liver was tender and enlarged to three finger-breadths below the right costal margin. The prostate was not enlarged.

Laboratory tests revealed a hemoglobin of 8 gm. per 100 cc., serum potassium of 8.7 mEq. per liter, serum sodium of 133 mEq. per liter, total serum carbon dioxide content of 9 mEq. per liter, blood urea nitrogen of 270 mg. per 100 cc. and serum creatinine of 20 mg. per 100 cc. A urinalysis showed a specific gravity of 1.011, a 3-plus reaction for albumin, 15 to 20 red blood cells, 10 to 15 white blood cells per high power field, and occasional granular and hyaline casts. The venous pressure (right arm) was 165 mm. of water. A roentgenogram of the chest revealed moderate cardiac enlargement to the left, pulmonary vascular congestion, and diffuse bilateral infiltration distributed in a "butterfly" configuration consistent with uremia and pulmonary edema. The electrocardiographic findings were compatible with severe hyperkalemia.

The immediate therapy consisted of an infusion of glucose, insulin, and sodium bicarbonate; digitalization; and oxygen by mask. Within one hour the serum potassium was lowered to 7.3 mEq. per liter. The patient regained partial motor function in his extremities and intercostal muscles. Shortly thereafter he was dialyzed on the artificial kidney for 5¾ hours. The postdialysis chemistries revealed a serum sodium concentration of 126 mEq. per liter, serum potassium of 3.3 mEq. per liter, and a total serum carbon dioxide content of 21 mEq. per liter. Blood urea nitrogen was 115 mg. per 100 cc., and the serum creatinine was 11.8 mg. per 100 cc. There was marked clinical and symptomatic improvement. Breathing was easier, and voluntary movement in the extremities strikingly improved. The lungs were clear, and a roentgenogram of the chest revealed marked reduction of hilar infiltration as well as narrowing of the cardiac shadow.

During the next 12 days the average daily urine output was 900 cc., and the average blood pressure was 200/100. Another dialysis was performed on the artificial kidney 13 days after admission because of laboratory and electrocardiographic evidence of hyperkalemia, and again a dramatic improvement was noted. However, 36 hours later, acute pulmonary edema developed secondary to acute cardiac failure that was refractory to the usual regimen of treatment (See Fig. 1, Part A).

An attempt was made to control the marked elevation in blood pressure. A continuous intravenous drip of 250 mg. of Arfonad in 300 cc. of 5% glucose in water was started at a rate of 1 mg. per minute. Within 30 minutes the blood pressure was lowered from 192/100 to 140/80 (Fig. 1, Part B). The patient commented that he could breathe much more easily. The cyanosis diminished, the respiratory rate slowed, the neck veins were less distended, and the pulse rate decreased from 130 to 100 per minute. Only a few scattered rales were audible. The infusion was discontinued after 21 hours. Within 30 minutes the patient's blood pressure was elevated to 165/87 and within one hour it reached pretreatment levels. All the objective and subjective signs of pulmonary edema returned. This was promptly relieved on readministration of the drug, which lowered the blood pressure to 130/70 (Fig. 2).

During the last 15 days of the patient's life, Arfonad was given intermittently for a total of 11 days with excellent control of the blood pressure (120 to 140/80 to 95) and almost complete relief of the pulmonary edema. The 11 days' treatment with Arfonad included 7 consecutive days of continuous administration of the drug. The rate of flow was very nearly constant during the period of therapy, and at no time was there any evidence of accumulated tolerance to the drug. The only untoward effects were photophobia due to fixed pupillary dilation and depression of the basal body temperature, which was promptly corrected by the application of external heat.

The urine output during the last 15 days of life averaged 200 cc. per day, and the patient became progressively more uremic and acidotic. (Arfonad did not affect a change in urinary volume.) Approximately 24 hours before death, the serum potassium was 7

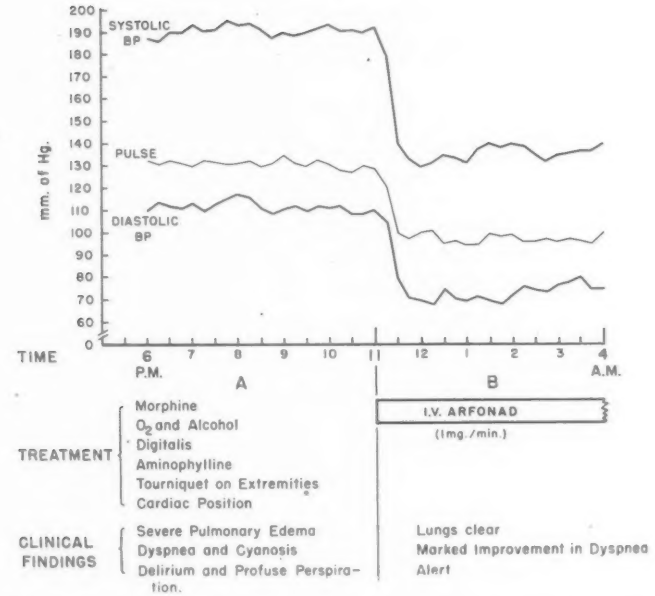


Fig. 1.—A. Pulmonary edema refractory to the usual methods of treatment. B. Blood pressure response to I.V. Arfonad with immediate clearing of pulmonary edema.

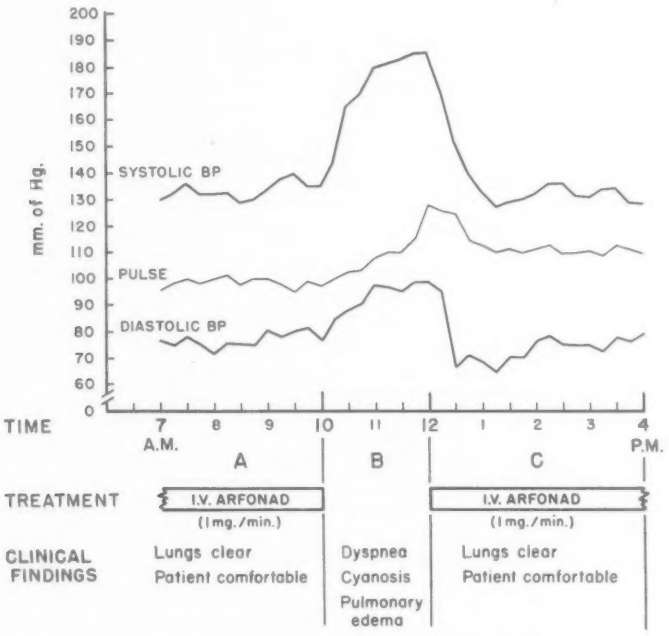


Fig. 2—A. and C. Blood pressure response and symptomatic relief during Arfonad therapy. B. Blood pressure elevation and return of symptoms on discontinuing Arfonad.

mEq. per liter, the total carbon dioxide content 24 mEq. per liter, and the serum creatinine 24 mg. per 100 cc. Further dialysis was not feasible, and the patient expired 30 days after admission following cardiac arrest, which was probably due to hyperkalemia. Arfonad was discontinued 10 hours before death.

NECROPSY FINDINGS. The kidneys weighed 225 and 220 gm. respectively and had a diffusely granular surface. They appeared edematous, and there was some narrowing of the cortex. On histologic examination, the typical changes of chronic glomerulonephritis were observed. The lungs were edematous and congested; they weighed 1700 to 1750 gm. respectively. There were 400 cc. of straw-colored pleural effusion in the right thoracic cage. The liver and spleen were enlarged secondary to congestion, but the heart was only slightly enlarged. Other significant changes were not noted.

Discussion. The relationship between peripheral vascular tone and acute pulmonary edema in hypertension has been demonstrated by Sarnoff *et al.*[2,4,7]. They found that peripheral vasodilation induced by spinal anesthesia in patients with acute pulmonary edema was followed by prompt improvement[5]. Presumably this was brought about by 1) the diminution in peripheral resistance against which the failing ventricle was working, and 2) a shift of blood from the pulmonary parenchyma to the peripheral vascular bed as a result of peripheral vasodilation. However, the occasional and unpredictable precipitous hypotension induced by spinal anesthesia indicated the need for a more easily controlled method of inducing peripheral vasodilation.

The continuous, graded administration of the ganglionic blocking agent, Arfonad, provided such a method in this case. The preparation was administered by intravenous drip for 7 consecutive days; altogether, the drug was given for 11 days. There was immediate objective and subjective improvement concomitant with a lowering in blood pressure, and this was maintained as long as the medication was given. Blood pressure levels were easily controlled by regulating the rate of infusion, and tolerance to the drug did not develop. The side effects were minimal and easily corrected.

Summary. Arfonad, a new ganglionic blocking agent, was used for 11 days in a patient who had chronic glomerulonephritis with uremia, hypertension, and pulmonary edema. The drug effectively decreased the blood pressure, and improved the signs and symptoms of severe pulmonary edema.

The hypotensive effects were readily controlled by regulating the rate of administration. Untoward reactions were minimal, and tolerance to the drug did not develop.

REFERENCES

1. **McCubbin, J. W.**, and **Page, I. H.**: J. Pharmacol. & Exper. Therap., **105**, 347, 1952.
2. **Nicholson, M. J.**, **Sarnoff, S. J.**, and **Crehan, J. P.**: Anaesthesiology, **14**, 215, 1953.
3. **Randall, L. O.**, **Peterson, W. G.**, and **Lehmann, G.**: J. Pharmacol. & Exper. Therap., **97**, 48, 1949.
4. **Sarnoff, S. J.**, and **Berglund, E.**: Am. J. Physiol., **170**, 588, 1952.
5. **Sarnoff, S. J.**, and **Farr, H. W.**: Anaesthesiology, **5**, 69, 1944.
6. **Sarnoff, S. J.**, **Goodale, W. T.**, and **Sarnoff, L. C.**: Circulation, **6**, 63, 1952.
7. **Sarnoff, S. J.**, and **Sarnoff, L. C.**: Ibid., **6**, 51, 1952.

STRESS AND GASTRIC SECRETION IN MAN. I. A STUDY OF THE MECHANISMS INVOLVED IN INSULIN HYPOGLYCEMIA

By Harry Shay, M.D.
PROFESSOR OF CLINICAL MEDICINE
DIRECTOR, FELS RESEARCH INSTITUTE

AND

David C. H. Sun, M.D., M.Sc. (Med.)
INSTRUCTOR IN MEDICINE, RESEARCH ASSOCIATE, FELS RESEARCH INSTITUTE

(From the Samuel S. Fels Research Institute and Temple University School of Medicine and Hospital, Philadelphia Pennsylvania)

The importance of stress in initiating peptic ulcer and in precipitating recurrences is now generally accepted. What the clinician can do to counteract the damaging effects of stress is quite another problem. Unfortunately, unlike the results possible in the patient with ulcerative colitis, psychotherapy in the management of the patient with peptic ulcer has not proved too effective. It is hoped, therefore, that if the physiological pathways through which stress deleteriously affects the ulcer patient could be determined then, perhaps, a more effective pharmacologic attack on the problem might be made.

The stellar roles that gastric hydrochloric acid and pepsin play both in initiating the original ulcer and in ulcer recurrence is generally conceded. The excellent studies of Gray and his associates[5] in man have supplied convincing evidence for the stimulatory effect of stress, adrenocorticotrophic hormone (ACTH) and adrenal corticoids on gastric acid and pepsin secretion. These investigators have demonstrated that uropepsin output in the urine, as well as pepsin and hydrochloric acid output in the stomach will be increased by any one of these agents. Furthermore, they have shown that neither intact vagi nor the gastrin mechanism is necessary for this stimulation to take place, for stress or ACTH effectively increases acid and pepsin secretion even after bilateral vagotomy and subtotal gastric resection. It appears reasonable to assume that whatever the mechanism through which hydrochloric acid and pepsin are stimulated by these agents, it represents, in part at least, a direct action on the gastric secretory cells.

Very important among the recent contributions to our understanding of the fundamental mechanism concerned in gastric secretion are the studies of Porter, Movius and French[11] and of French, Longmire, Porter and Movius[3]. These investigators, using monkeys, measured changes in the pH of gastric secretion after electrical stimulation of the nuclei of the anterior hypothalamus at the level of the optic chiasma and of the posterior hypothalamus at the mammillary bodies or tuber cinereum. When they stimulated the former, the fall in pH of gastric secretion reached its maximum ½ to 1 hour after stimulation and returned to prestimulation levels (pH 4 to 6) within 3 hours. This response failed to appear in an animal with bilateral vagotomy. Stimulation of the posterior hypothalamic nuclei produced a decrease in pH of gastric secretion which, however, did not begin until 2 to 2½ hours after stimulation,

reached the lowest pH levels in 3 hours and took 5 hours to return to prestimulation values. This response failed to appear in animals previously adrenalectomized. Bilateral vagotomy and adrenalectomy followed by stimulation of either or both areas resulted in pH values of gastric secretion that remained at basal values throughout the experiment.

French and his associates[3] have reproduced in the monkey the increase in gastric acid secretion following the administration of ACTH and cortisone, shown to occur in man in the experiments of Gray *et al.* They further confirmed that intact vagi are unnecessary for this action to take place but that the adrenals are essential for ACTH to produce its effect.

Gray *et al.*[5] and Porter[11] and his associates have evolved hypotheses for the action of stress in causing an increase in gastric secretion. Hume[6] postulated the liberation of an anterior hypothalamic hormone following stimulation of the hypothalamus. This hormone, Hume believes, acts on the anterior hypophysis with the liberation of ACTH. Based on Hume's hypothesis, Gray has offered a schema to show how stress increases acid and pepsin secretion in the stomach. This schema proposes that the anterior hypothalamic hormone of Hume, liberated by the effect of stress on the hypothalamus, stimulates the anterior pituitary to produce ACTH which, in turn, stimulates the adrenal cortex to produce adrenal corticoids and these act on the gastric mucosa to stimulate secretion of acid and pepsin. It is, however, impossible to reconcile the liberation of an anterior hypothalamic hormone, suggested by Hume to act in the manner pictured by Gray, with the results of Porter and his associates. If the Hume hypothesis applies to the monkey, then Porter, French *et al.* should have produced a double or a composite type of gastric secretory curve by stimulation of the anterior hypothalamus. These investigators actually did produce a composite type of gastric acid curve, but through

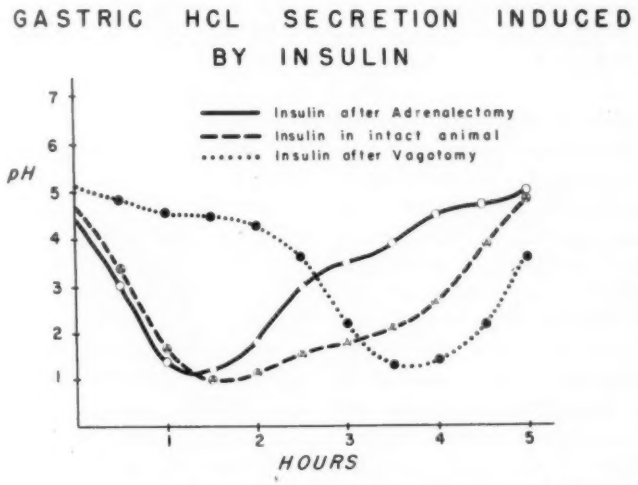


Fig. 1.—Gastric acid secretory response in monkey to insulin hypoglycemia in intact animal and after bilateral vagotomy and adrenalectomy respectively. (Porter, Movius and French, courtesy of Surgery.)

the action of insulin hypoglycemia. They were further able to resolve this composite curve into an early and a late component deriving, respectively, from stimulation of the anterior and posterior hypothalamus (Fig. 1).

From their studies Porter, French *et al.* have pictured stimulation of the posterior hypothalamus to increase gastric secretion by stimulation of the anterior pituitary directly with the release of ACTH. This explanation is open to question since the evidence currently available indicates that pathways to the pituitary from the posterior hypothalamus lead only to the posterior pituitary.

In 1930, Beattie, Brow and Long[2] showed that stimulation of the posterior hypothalamus gave rise to epinephrine secretion. More recently, Vogt[15], by direct measurement of the output of adrenal cortical hormone after the intravenous injection of epinephrine in dogs, showed that the rate of secretion rose rapidly and continued for some time after quantities of epinephrine that may be regarded as within the physiological rate of secretion of the adrenal medulla. Long and Fry[9] and later Gershberg, Fry, Brobeck and Long[4] observed, in normal rats, that the subcutaneous, intravenous or intramuscular injection of epinephrine in quantities of the order of a few micrograms was followed within an hour by a well marked fall in both the cholesterol and ascorbic acid content of the adrenal gland. Recently, Long[7] has demonstrated that the direct application of epinephrine to anterior pituitary lobe tissue is followed by ACTH release. Long hypophysectomized rats and then implanted into the anterior chamber of one eye of these animals a piece of anterior pituitary lobe from a donor animal. After a sufficient period had been allowed for the growth of the transplant, the response of this tissue to the subcutaneous injection (20 micrograms) of epinephrine was determined. In those animals in which an eosinopenia occurred, indicating a viable transplant, a very small quantity of epinephrine (0.2 microgram) was later injected into the anterior chamber of the eye bearing the pituitary transplant. In all 7 an eosinopenia of equal magnitude to that produced by subcutaneous epinephrine (20 micrograms) was observed. Similar injections of 0.2 microgram of epinephrine into the normal eye failed to produce any fall in eosinophils. Finally, the eye bearing the transplant was removed, after which no eosinophil response to subcutaneously injected epinephrine (20 micrograms) was obtained.

The results from Long's laboratory, coupled with those of Porter, French and their associates with insulin hypoglycemia prompted us to study the prolonged gastric secretory effect (6 hours) of insulin hypoglycemia in man, in order to determine whether man too would show a double response curve to insulin hypoglycemia and if so, could we resolve the response into its respective components, especially since Porter, French and their associates obtained a gastric pH curve in monkeys following epinephrine injection that was very similar to that which followed posterior hypothalamic stimulation alone.

Experimental Method. We employed the same method which we used in a study of parasympathetic blocking agents on gastric secretion[14]. The patient fasts for 12 to 14 hours and receives no medication the day before the test. A Rehfuss tube is introduced into the stomach and, under fluoroscopic control, the tip of the tube is placed in the antrum. The tube, after slack is withdrawn, is fixed at lip level with adhesive to the chin. The patient remains in the supine position throughout the test and is instructed to expectorate all saliva. The stomach is emptied completely and aspiration of the gastric

contents at a negative pressure of 30 inches of water is continued throughout the test period. Fifteen-minute fractions are collected for one hour before and for 5 hours after the administration of the test substances. These are physiological saline for the control test, insulin alone, Regitine alone and insulin with Regitine. Mucus or bile, or both, in the gastric contents are noted. Before the end of each 15-minute collection period, complete gastric emptying is assured by placing patient on back and each side for one minute.

The volume of each 15-minute sample is measured and free and total acidity are determined by titration with N/50 sodium hydroxide, using Töpfer's reagent and phenolphthalein as indicators. The pH of the gastric contents is determined using a Beckman pH meter and glass electrode.

Blood sugar determinations are made on fasting, 10, 20, 30, 60, 90 and 120-minute specimens and then at hourly intervals after the administration of the test substances. Eosinophil counts are done before and at 4 or 5 hours, or both, after the administration of the test substance.

Five patients with chronic duodenal ulcer were used in this study. Each patient served as his own control. The following studies were done on different days in the same patient:

1. Basal secretion: Five-hour basal secretion was studied on four different days in 3 of 5 patients.

2. Insulin hypoglycemia: The effect of insulin hypoglycemia upon gastric acid output was investigated in all. Regular insulin, in a dose of 15 to 25 units, was given intravenously.

3. The effect of insulin hypoglycemia and Regitine, an adrenolytic and sympatholytic drug, upon gastric acid output was studied in all. Regitine, in a dose of 10 mg. dissolved in 100 cc. of sterile physiological saline, was given intravenously at a rate of 15 drops per minute. Five minutes after starting the Regitine infusion, regular insulin was administered intravenously. The same dose of insulin was used throughout the tests on any one patient.

4. Effect of Regitine on basal secretion: the effect of Regitine alone on basal secretion was studied in 3 patients.

5. The effect of insulin hypoglycemia alone and with Regitine before and 15 days after bilateral vagotomy and subtotal gastrectomy was studied in one patient.

Results and Discussion. Figure 2 shows the results in a patient, L. O., with duodenal ulcer. The dotted line (open triangles) represents the average of 4 studies of basal secretion of total acid output in this individual over 5-hour periods on different days; the solid line, the response after insulin (I), the curve of acid output showing that secretion had gotten well under way after the first hour, reached a peak between 1½ and 2 hours, a second peak between 3 and 3½ hours and perhaps a third peak between 4 and 5 hours after the insulin administration. The broken line (open circles) represents the result after insulin plus Regitine (I&R). The early rise in secretion with its peak at 1½ to 2 hours remains, while the late secretion is now prevented by the Regitine. Blood sugar and eosinophil response are noted at the bottom of the chart. A similar curve showing early and late peaks of acid secretion was obtained in all of these 5 patients after insulin hypoglycemia. One of the 5 patients failed to show inhibition of the late secretory response when insulin and Regitine were administered simultaneously. Regitine alone had no significant effect on the basal gastric secretion in all 3 patients studied.

The pH values as indicated under experimental method were recorded for each 15-minute specimen. When these values were plotted the increase in gastric acid secretion produced by the insulin hypoglycemia is evidenced by the drop in pH and this drop is sustained throughout, approximately a 4-hour period after insulin hypoglycemia is produced. Plotting the pH values alone, however, does not disclose the different periods of increased acid secretion and masks the peaks of acid output which are uncovered when the total acid output is plotted (Figs. 2 and 3). This did not obtain to the same degree in the results in monkeys obtained by Porter, French and their associates and rightly so because the col-

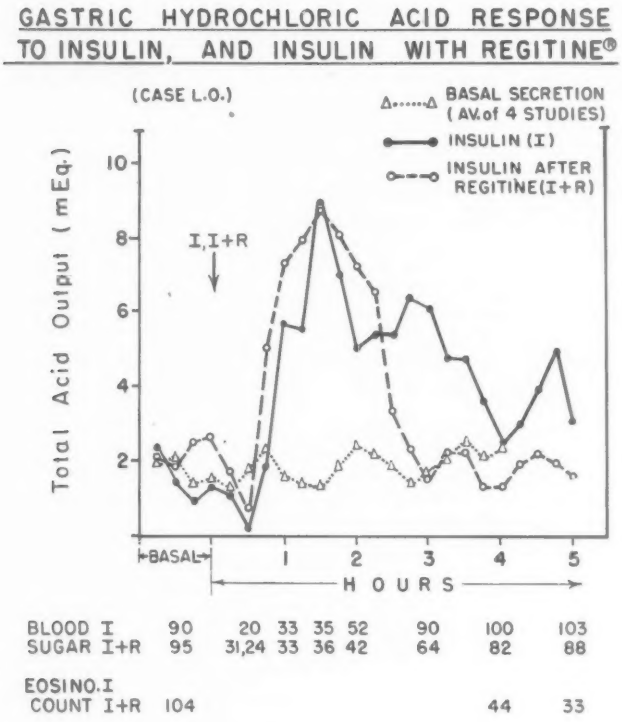


Fig. 2.—Curves of total acid output. Basal secretion, after intravenous insulin and after insulin and Regitine. Blood sugar curves during each study with insulin and the eosinophil response after insulin and Regitine.

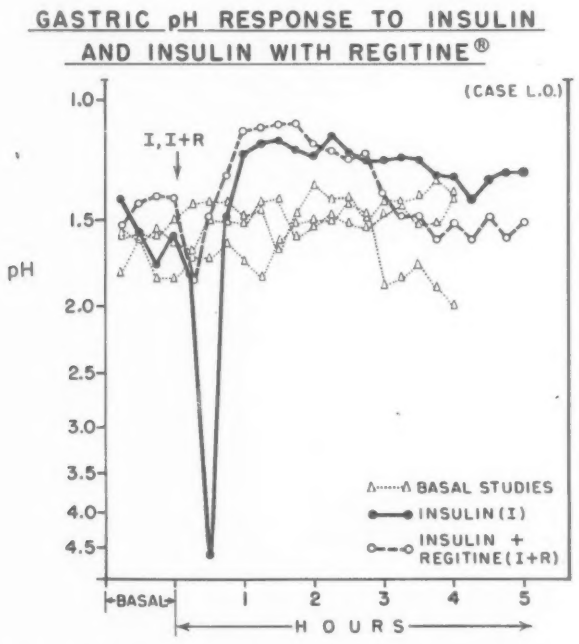


Fig. 3.—pH values during periods of tests illustrated in Fig. 2.

lection of gastric specimens in the monkey and in our human experiments was different. In the experiments in monkeys pH determinations were made on *aspirated samples* obtained through a Levin tube, before and every half-hour after administration of the test substance, for 5 to 7 hours. Such a procedure sets up physicochemical conditions where buffering mechanisms and gastric emptying will influence changes in pH of the gastric contents somewhat differently from one in which all of gastric secretion is aspirated continuously. With the latter method, although the rate of secretion may change considerably, the pH may not be altered too greatly by this change unless it is very marked. This may also be the explanation for the composite type curve obtained by Porter, French *et al.* after insulin hypoglycemia in monkeys as seen in their illustration reproduced in Fig. 1. It is possible that total acid output if measured after insulin in monkeys would, too, show the early and late curves of secretion as we have found in man, into which Porter *et al.* could resolve the gastric secretory response to hypoglycemia after insulin in the monkey. Furthermore, Regitine is seen in Fig. 3 to block the late portion of the acid secretory response as indicated by the pH curve. However, if the change in the pH curve is compared with the change registered in

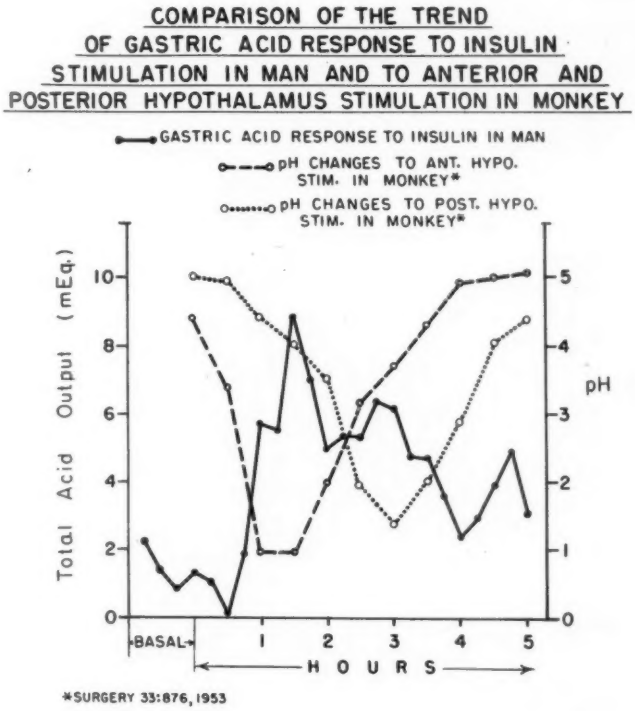

COMPARISON OF THE TREND
OF GASTRIC ACID RESPONSE TO INSULIN
STIMULATION IN MAN AND TO ANTERIOR AND
POSTERIOR HYPOTHALAMUS STIMULATION IN MONKEY
GASTRIC ACID RESPONSE TO INSULIN IN MAN
pH CHANGES TO ANT. HYPO. STIM. IN MONKEY*
pH CHANGES TO POST. HYPO. STIM. IN MONKEY*
Total Acid Output (mEq.)
pH
BASAL
HOURS
*SURGERY 33:876, 1953

Fig. 4.—Shows the close parallelism in the early and late gastric secretory response to insulin hypoglycemia in man to pH curves in monkeys resulting from stimulation of the anterior and posterior hypothalamic nuclei respectively.

total acid output (Fig. 2) the effectiveness of Regitine in blocking the adrenal phase of gastric secretion becomes more apparent from the latter.

In Fig. 4 we have combined the curve of total acid output after insulin in patient L. O. with the pH curves

Attempts to inhibit the early curve of gastric secretion after insulin in man with parasympathetic blocking agents did not prove satisfactory. In order to relate this curve in man to stimulation of the vagal nuclei, the mechanism heretofore accepted as the total mech-

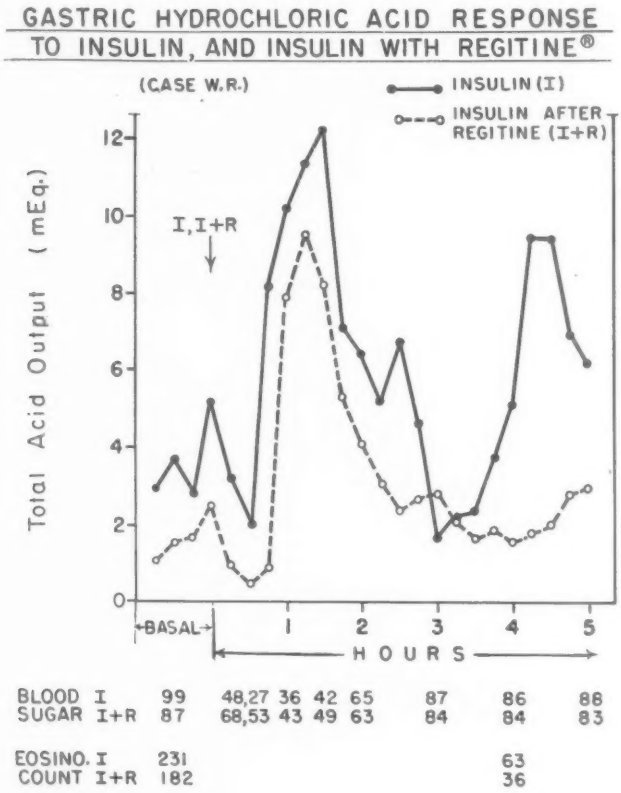

GASTRIC HYDROCHLORIC ACID RESPONSE
TO INSULIN, AND INSULIN WITH REGITINE®
(CASE W.R.)
INSULIN (I)
INSULIN AFTER REGITINE (I+R)
Total Acid Output (mEq.)
I, I+R
BASAL
HOURS
BLOOD SUGAR I 99 48,27 36 42 65 87 86 88
I+R 87 68,53 43 49 63 84 84 83
EOSINO. COUNT I 231 63
I+R 182 36

Fig. 5.—Acid secretory response, blood sugar curves and peripheral eosinophil counts in a patient with a duodenal ulcer after insulin and insulin plus Regitine, before operation.

of acid secretion in the monkey obtained by Porter, French and their associates, after stimulation of the anterior hypothalamus (early curve) and after stimulation of the posterior hypothalamus (late curve). The correspondence of these curves with the peaks in the curves of total acid output in patient L. O. is very striking.

anism through which insulin hypoglycemia stimulates gastric secretion, we studied the response under our experimental conditions, in a patient with duodenal ulcer before operation and again after subtotal gastrectomy and bilateral vagotomy. These results are illustrated in Figs. 5 and 6. In Fig. 5 (Patient W. R.) the solid line, the

acid output response after insulin alone, again revealed a response similar to that of patient L. O., except that the second of the late curves is the most prominent of the two. Regitine (broken line) again blocks both late curves leaving the early one essentially unaffected. In Fig. 6 is the response in this patient after operation. Since subtotal gastrectomy and vagotomy would be followed by a marked decrease in the rate of gastric secretion, the curves in Fig. 6 were made evident by altering the scale used in the preceding Figures 2 to 5 for illustration. In this way we are able to show that the solid line (Fig. 6) representing total acid output fails to contain the early curve of secretion with its peak at 1¾ hours after insulin seen in Fig. 5 obtained before operation and now shows only late peaks which are again eliminated by the administration of Regitine with the insulin (broken line).

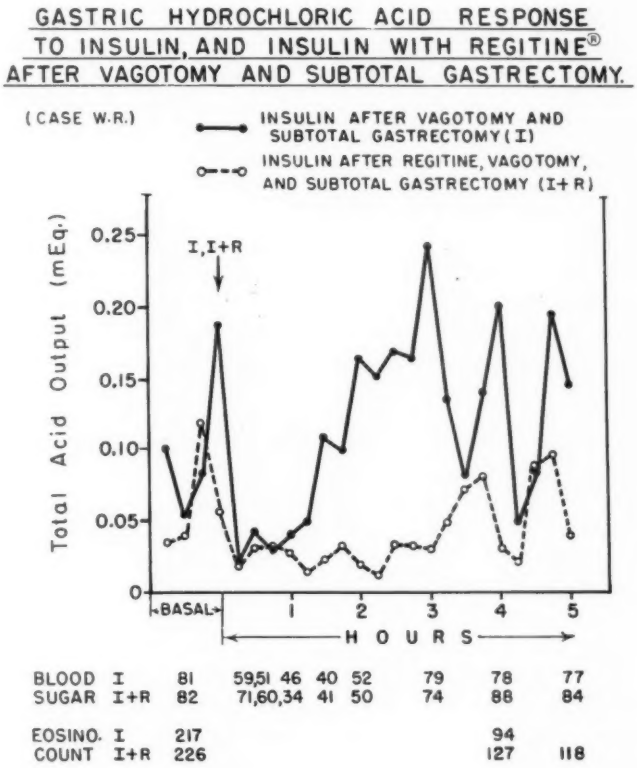


Fig. 6.—Response in same patient after subtotal gastrectomy and bilateral vagotomy. Note absence of early peak of secretion after insulin present in Fig. 5.

Our results in this patient indicate that for the action of insulin hypoglycemia to produce the late curve or curves of gastric secretion, neither intact vagi nor the gastrin mechanism are necessary, findings that parallel those obtained by Gray *et al.* with re-

spect to these mechanisms in the action of ACTH to stimulate secretion by the stomach. By inference from the studies of Porter, French *et al.* in the monkey this late secretion in man, too, represents an adrenal phase of gastric secretion.

The action of Regitine in blocking the late secretion of insulin hypoglycemia administered as it was in the dosage and at a rate at which its action should have been almost entirely if not entirely adrenergic blocking alone, suggests that adrenalin liberation was involved in the hypoglycemic action produced by the insulin and that the liberated adrenalin was intimately concerned in some way in the resultant stimulation of gastric secretion. In view of the results of Long[7] and the part that adrenalin can play in stimulation of the anterior pituitary, we would suggest the schema represented in Fig. 7. One of us[13] (H.S.) has recently indicated that because neural pathways from the posterior hypothalamus to the pituitary go only to the posterior pituitary and not to the anterior, that the posterior pituitary in response to the stress effect of insulin hypoglycemia may be involved in the pathways through which adrenalin is subsequently liberated by the adrenal medulla. Further study of available neurophysiological evidence[1], however, makes us feel that the pathway by way of the sympathetic is more likely. A problem arises even here since French, *et al.* found, in the monkey, that while an adrenergic blocking agent SKF 501 will block the late gastric secretory response to insulin, blockade of cephalic sympathetic outflow by cervical spinal cord section does not affect the late secretory response. Furthermore, Vogt[16] found in rats that pituitary-adrenal discharges can be evoked by insulin in demedullated animals. French *et al.*, convinced that epinephrine also plays an important role in the production of the late gastric secretory response to insulin hypoglycemia in monkeys, have pictured this to come about by insulin hypoglycemia stimulating the adrenal medulla and the epinephrine so produced to stimulate the posterior hypothalamus. For this purpose, too, the evidence is not clear, for it is not at all certain that epinephrine will act as a stimulus to the hypothalamic centers. In fact there is some evidence[8,10] that it actually may decrease the response of these centers. Were it not for the fact that both in the monkey and in man the late gastric secretory response to insulin hypoglycemia is blocked by an adrenergic blocking agent one might seek an explanation for a possible pathway in the anterior pituitary stimulation by a posterior hypothalamic hormone reaching it through a portal circulation suggested by Scharrer[12]. This mechanism, however, still lacks confirmation and it would also not explain the epinephrine part of the cycle which now appears to have been demonstrated in both monkey and man for the late phase of gastric secretion produced by insulin hypoglycemia.

Another of our results of interest is the ability of Regitine to block the gastric secretory response, in which epinephrine release appears to be involved yet is unable to alter the eosinophil response.

Our experiments, thus far, we believe, warrant the conclusion that the stress stimulus supplied by insulin hypoglycemia in its effect on late curves of gastric secretion can be blocked in man as in the monkey by adrenergic blocking agents. It is reasonable to suggest then that epinephrine is liberated somewhere in the response to hypoglycemia and that the epinephrine is important in the release of ACTH to stimulate ACH production and its

effect in turn on gastric secretion. Although the exact pathways for man or monkey through which adrenalin release after hypothalamic stimulation occurs have not been completely defined and any pathways at present suggested will need to be modified by new evidence, the important fact, however, remains that if the stress effect produced by insulin hypoglycemia is representative of the action of stress phenomena in general or if even representative of only one form of the stress mechanism, then our results would indicate that in this form, at least, epinephrine is released and so perhaps suggest a beginning for a pharmacodynamic approach to the problem of stress in peptic ulcer.

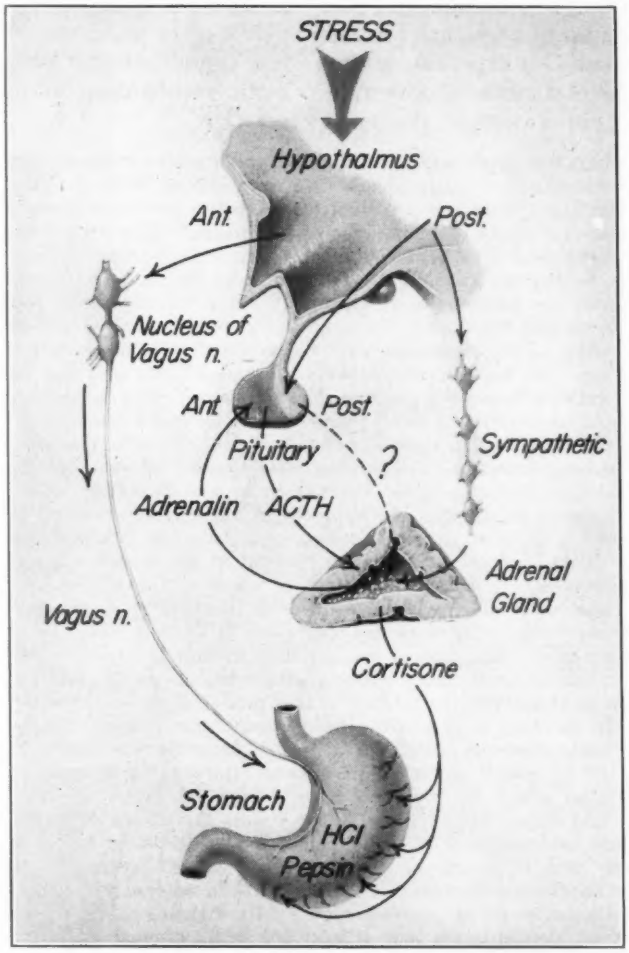


Fig. 7.—Schematic representation for a working hypothesis of the sequence of events responsible for the early and late curves of gastric secretion stimulated by insulin hypoglycemia.

Summary. Evidence that stress, ACTH, and cortisone stimulated gastric secretion in man was presented by Gray

and his coworkers. More recently Porter, French and their associates have demonstrated in monkeys that the stress effect of insulin hypoglycemia acting on the posterior hypothalamus initiated reactions that resulted in increased gastric acid secretion and that intact adrenals were necessary for this response to occur. Our experiments offer support for a similar mechanism in man. Furthermore, our evidence points to the probability that adrenalin is liberated in the stress effect of insulin hypoglycemia and plays an important part in the cycle that results in the stimulation of gastric secretion. We believe that it will be necessary to consider an adrenal phase of gastric secretion in the peptic ulcer problem and that this phase is a significant part of the harmful somatic mechanisms activated by stress reactions.

ADDENDUM. Since this paper was submitted for publication an opportunity arose to investigate an important segment of this problem. We were able to study the gastric acid secretory response to insulin hypoglycemia in a patient (H.S.) before and after bilateral total adrenalectomy for recurrent and metastatic carcinoma of the breast.* The results are shown in Figure 8. The right adrenal had been removed shortly before she became available for the gastric secretory studies, so that our initial study represented by the solid line represents the response of this patient with one intact adrenal gland. This line represents the total acid output to insulin hypoglycemia and shows an early peak in acid secretion between 1 and 1½ hours after insulin corresponding to the peak that we have demonstrated above to be dependent upon intact vagus nerves. The second peak between 1½ and 2 hours and the third peak between 2 and 2½ hours probably both belong, as we shall see subsequently, to the late phase of gastric secretion stimulated by the hypoglycemia which, if the mechanisms concerned for their production in man, is the same as that demonstrated by Porter, French *et al.* for monkeys, should be dependent on intact adrenals. Our studies after the second adrenal was removed in this patient show that this similarity of mechanisms in man and monkey exists. Because of the greatly increased insulin sensitivity to be expected in the adrenalectomized patient, the insulin test was performed with great caution 5 weeks after complete bilateral adrenalectomy. The patient weighed 50 kg. before and after the removal of the second adrenal. The use of 15 units of insulin intravenously before operation then involved a dose of 0.3 u/kg. (blood sugar values A). The dose of insulin first tested after the bilateral adrenalectomy was 1/40 u/kg. The gastric acid secretory response to this total dose (1.25 units) of insulin is shown by the dotted line and triangles. This dose of insulin failed to stimulate acid secretion over a 3-hour period of the test and also failed to produce a pronounced hypoglycemia (Blood sugar values B) for as long as or at any time as marked as that produced by the 15 units of insulin before adrenalectomy. In an effort to produce a hypoglycemic curve nearly comparable to that produced by the 15 units of insulin before the operation, the study was repeated using 1/30 u/kg. (total dose of 1.67 u) which produced the acid secretory curve illustrated by the dash and dot line (Blood sugar values C) and again using 1/20 u/kg. (total dose 2.5 u) illustrated by the broken line and open circles (Blood sugar values D). Each of these doses of insulin produced a gastric acid secretory response that was very pertinent to our problem, for each produced an early peak of gastric secretion between 1 and 1½ hours after the insulin, corresponding to the early (vagal) curve seen before the second adrenal was removed and thereafter produced no additional peaks of acid secretion for the balance of the 6-hour test period. In this patient we have demonstrated that at least one intact adrenal gland is necessary for the late phase of gastric secretion to appear after insulin hypoglycemia.

These results, we believe, lend credence to our discussion regarding the significance of the Regitine action described above and the probable role played by the release of adrenalin by insulin hypoglycemia, to in turn set in motion the series of events that result in the stimulation of gastric secretion by ACH.

The response of circulating eosinophils to insulin hypoglycemia before and after bilateral total adrenalectomy are shown at the bottom of the chart. Before the operation there was a significant fall of 80% in circulating eosinophils after an adequate hypoglycemia stimulus, while after the second adrenal was removed a similar adequate hypoglycemic response failed to produce eosinopenia.

*We are indebted to Dr. Karl C. Jonas for permitting us to study his patient (H.S.) before and after he removed the second adrenal gland.

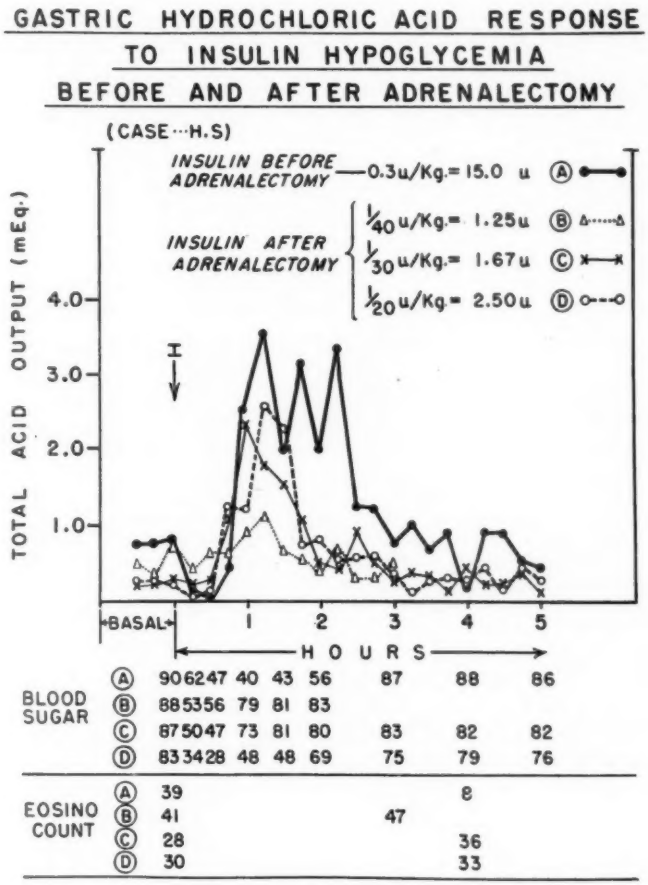


Fig. 8.—Total gastric acid response, blood sugar curves and eosinophil counts after insulin hypoglycemia in a patient with metastatic carcinoma of the breast after the removal of one adrenal and after total adrenalectomy.

ACKNOWLEDGMENT. The authors gratefully acknowledge the technical assistance of R. Smiley Pattinson, B.S., M.T., and Jean Atwater, B.S., M.T.

REFERENCES

1. **Beattie, J.**: Canad. Med. Assn. J., **26**, 400, 1932.
2. **Beattie, J., Brow, G. R.,** and **Long, C. N. H.**: Proc. Roy. Soc., Series B., **106**, 253, 1930.
3. **French, J. D., Longmire, R. L., Porter, R. W.,** and **Movius, H. J.**: Surgery, **34**, 621, 1953.
4. **Gershberg, H., Fry, E. G., Brobeck, J. R.,** and **Long, C. N. H.**: Yale J. Biol. & Med., **23**, 32, 1950.
5. **Gray, S. J., Ramsey, C., Reifenstein, R. W.,** and **Benson, J. A.**: Gastroenterology, **25**, 156, 1953.
6. **Hume, D. M.**: J. Clin. Invest., **28**, 790, 1949.
7. **Long, C. N. H.**: Endocrinology. Ciba Foundation Colloquia, **4**, 145, 1952. New York: The Blakiston Co., 1952.

8. Idem: In discussion. Ciba Foundation Colloquia, **4**, 100, 1952. New York: The Blakiston Co., 1952.
9. **Long, C. N. H.**, and **Fry, E. G.**: Proc. Soc. Exper. Biol. & Med., **59**, 67, 1945.
10. **Merrazzi, A. S., Jr.**: The Biology of Mental Health and Disease. New York: P. B. Hoeber, 1952, p. 376.
11. **Porter, R. W., Movius, H. J.**, and **French, J. D.**: Surgery, **33**, 875, 1953.
12. **Scharrer, E.**, and **Scharrer, B.**: Presented at Laurentian Hormone Conference, September, 1953.
13. **Shay, H.**: Gastroenterology, **26**, 316, 1954.
14. **Sun, D. C. H., Shay, H.**, and **Ciminera, J.**: J. Am. Med. Assn., in press.
15. **Vogt, M.**: J. Physiol., **103**, 317, 1940.
16. Idem: Ibid., **114**, 222, 1951.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence, should be sent to the Editor, DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa. Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. The recommendations of the American Medical Association Style Book should be followed. REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100.

BINDERS AVAILABLE FOR YOUR COPY OF

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

In response to numerous requests, we can now offer subscribers attractive and sturdy binders large enough to hold six issues of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES.

These binders will not only help to preserve your copies of The Journal, but will prove a definite asset to the appearance of your library. Binders are dark blue fabrikoid, with the name: AMERICAN JOURNAL OF THE MEDICAL SCIENCES, stamped in gold. Price, $2.00 each.

SIMULTANEOUS PRESSURE MEASUREMENTS IN THE HEPATIC VENULE AND PORTAL VENOUS SYSTEM IN MAN

By George E. Welch, M.D.
CLINICAL INSTRUCTOR IN MEDICINE, TULANE UNIVERSITY SCHOOL OF MEDICINE

Robert Emmett, M.D.
CLINICAL INSTRUCTOR IN SURGERY, LOUISIANA STATE UNIVERSITY SCHOOL OF MEDICINE

Claude C. Craighead, M.D.
CLINICAL INSTRUCTOR IN SURGERY, LOUISIANA STATE UNIVERSITY SCHOOL OF MEDICINE

George Hoeffler, M.D.
RESIDENT IN RADIOLOGY, CHARITY HOSPITAL

Donovan C. Browne, M.D.
ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, TULANE UNIVERSITY SCHOOL OF MEDICINE

AND

Irving Rosen, M.D.
RESIDENT IN MEDICINE, TOURO INFIRMARY

(From the Departments of Medicine and Surgery, Tulane University School of Medicine and the Louisiana State University School of Medicine, and the Browne-McHardy Clinic, New Orleans, Louisiana)

Portal hypertension has always posed a problem in diagnosis and correction. Assessment of portal pressure by occlusive hepatic venular catheterization has been proposed by Meyers and Taylor[1] and more recently by Paton, *et al.*[2]. The present studies were undertaken to compare pressures obtained simultaneously in the hepatic venule and the portal system in order to substantiate the validity of the method in measuring portal pressure.

Methods. Simultaneous pressure determinations were made in an hepatic venule and the portal vein, employing the method of hepatic venule catheterization of Meyers and Taylor[1], and by the portal vein at laparotomy in 10 reclining adults. Saline manometer pressures were read from a zero point 9 cm. above the posterior chest wall. Occlusive hepatic venule pressures were first obtained in the preoperative state. The patients were then moved to the operating room with the catheter in the hepatic venule where, under general endotracheal ether anesthesia, the abdomen was opened and simultaneous pressure determinations were made direct in the portal vein or one of its tributaries and again in the hepatic venule through the previously introduced catheter.

Results. PREOPERATIVE STUDY. In the 6 patients without liver disease, the mean hepatic venule pressure was 16.8 cm. of physiological saline solution. In the free large hepatic vein the average pressure was 11.6 cm. Thus the average gradient difference as between venule and vein is 5.2 cm. (Table 1).

In the 4 patients with proven liver disease (biliary cholangitis, early Laennec's cirrhosis, and 2 cases of carcinoma metastatic to the liver) but without clinical evidence of portal hypertension, the mean hepatic venule pressure was 19.2 cm. of normal saline. The mean hepatic vein pressure in this group was

13.2 cm., yielding a gradient of 5.9 cm. (Table 1).

STUDY AT OPERATION. In the patients without liver disease the mean hepatic venule pressure was 21.8 cm. of physiological saline solution representing an average rise of 5 cm. when compared with their preoperative pressure (Fig. 1). The average hepatic vein pressure was 20.3 cm. with a gradient of 1.5 cm. The direct portal vein pressure averaged 20.3 cm. of normal saline representing a slightly reversed gradient of 1.5 cm. of normal saline when compared with the hepatic venule pressure (Table 1). This is probably due to the particular technique employed, but may represent the opening of hepatic arterial-venule shunts. The mean gradient between the preoperative hepatic venule pressure and the direct portal vein pressure was 3.5 cm. of physiological saline solution (Table 1).

TABLE 1.—SIMULTANEOUS PRESSURE MEASUREMENTS (IN CENTIMETERS OF PHYSIOLOGICAL SALINE SOLUTION) IN THE HEPATIC VENULE AND PORTAL VENOUS SYSTEM IN MAN

	Preoperative	*At Operation*
NORMALS		
Hepatic Venule	12.4–21.4 (16.8)	16.0–29.1 (21.8)
Hepatic Vein	5.4–14.0 (11.6)	14.6–24.0 (20.3)
Gradient	2.0–8.2 (5.2)	1.2–5.1 (3.1)
Portal System	—	11.8–25.3 (20.3)
		−3.4–+5.5 (+1.5)
ABNORMALS		
	Preoperative	*At Operation*
Hepatic Venule	15.5–21.4 (19.2)	22.5–37.3 (29.2)
Hepatic Vein	7.9–18.6 (13.2)	17.8–25.4 (20.7)
Gradient	2.8–11.4 (5.9)	3.5–11.9 (8.5)
Portal System	—	26.0–37.3 (30.9)
Gradient	—	0.0–3.5 (1.7)

In the group with liver disease the average hepatic venule pressure was 29.2 cm. of physiological saline solution. The mean hepatic vein pressure was 20.7 cm., with a gradient of 8.5 cm. The mean direct portal vein pressure was 30.9 cm. of physiological saline solution, with an average gradient of 1.7 cm., when compared with the occluded hepatic venule pressure in this same group. The mean gradient between the preoperative hepatic venule pressure and the direct portal vein pressure at operation was 11.7 cm.

The pertinent pressure values with means and extremes are presented in Table 1.

When the individual pressure values of the hepatic venule and portal system at operation are plotted graphically a relatively linear distribution is evident even in this small series (Fig. 1). The coefficient of correlation between the pressures in the hepatic venule and the portal vein is 0.86 ± 0.77, with the probability of a chance relationship lying between 0.01 and 0.001.

In all but Case 3 there was a rise in hepatic venule pressure at operation, and this was greater in the abnormal group (Fig. 2). Statistically these observations are not significant, since there are so few cases in the series.

Conclusions. Occlusive catheterization of the hepatic venule may be used to assess pressures in the portal system in patients with and without liver disease. An approximate linear relationship exists between portal pressure and occlused hepatic venule pressure when measured simultaneously.

There is a rise in hepatic vein and hepatic venule pressure at operation which is greater in the abnormal group.

The caliber of portal system vessel had no significant effect on the pressure reading, provided the portal vein or one of its larger tributaries was employed.

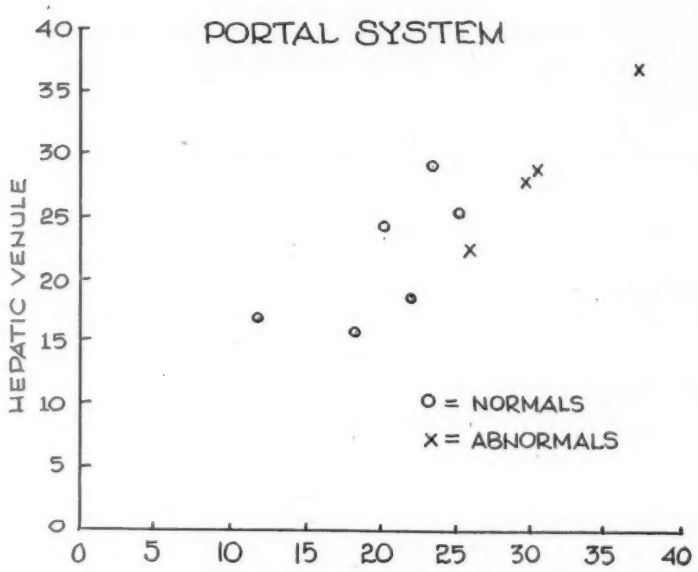


Fig. 1.—All pressures in cm. of physiological saline solution.

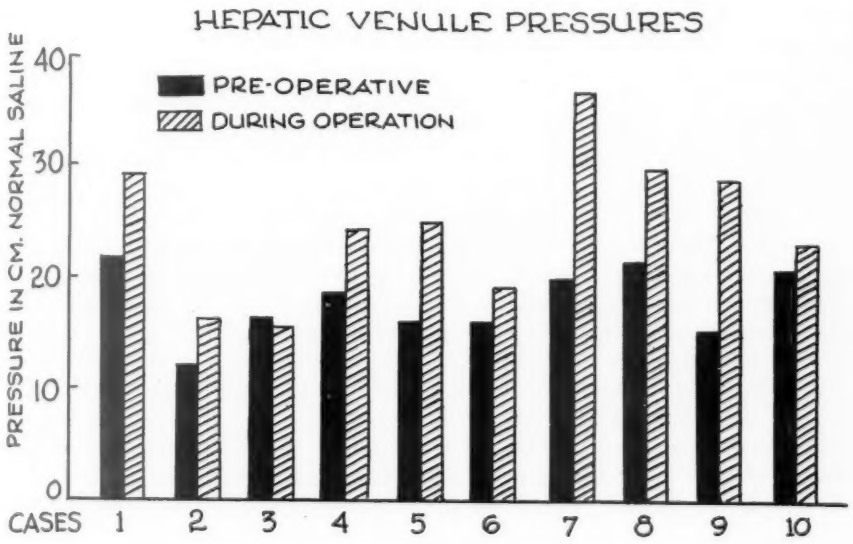


Fig. 2.

REFERENCES

1. Meyers, J. D., and Taylor, W. J.: J. Clin. Invest., 30, 662, 1951.
2. Paton, A., Reynolds, T. B., and Sherlock, S.: Lancet, 1, 918, 1953.

N-HYDROXYETHYLETHYLENEDIAMINE TRIACETIC ACID, VERSENOL, IN THE TREATMENT OF HEMOCHROMATOSIS

By Marvin J. Seven, 1st. Lt., MC, USAR*
FORMERLY, RESIDENT IN MEDICINE, PHILADELPHIA GENERAL HOSPITAL

Harry Gottlieb, M.D.
RESIDENT IN MEDICINE, PHILADELPHIA GENERAL HOSPITAL

Harold L. Israel, M.D
ASSOCIATE PROFESSOR OF MEDICINE, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND ASSISTANT VISITING PHYSICIAN, PHILADELPHIA GENERAL HOSPITAL

John G. Reinhold, Ph.D.
ASSOCIATE PROFESSOR OF CHEMISTRY, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, AND CONSULTANT BIOCHEMIST, PHILADELPHIA GENERAL HOSPITAL

AND

Martin Rubin, Ph.D.
ASSOCIATE PROFESSOR, CHEMO-MEDICAL RESEARCH INSTITUTE, GEORGETOWN UNIVERSITY

(From the Department of Medicine, Philadelphia General Hospital; The Pepper Laboratory of the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; and the Departments of Chemistry, Georgetown University School of Medicine and Graduate School, Washington, D. C.)

Hemochromatosis is a disorder of iron metabolism characterized by abnormal absorption of iron from the small intestine occurring principally in males but occasionally encountered in postmenopausal women. The disease may be clinically manifested by skin pigmentation, weakness, hepatomegaly, diabetes, myocardosis, decreased libido, decreased axillary and pubic hair, and testicular atrophy. Histologically, there is increased melanin deposition in the skin and deposition of hemosiderin in nearly all of the tissues of the body[1,4,7,14,17]. Iron must increase 10 to 20 mg. per 100 gm. of liver tissue before hemosiderin is microscopically observed[8]. Unlike hemosiderosis where iron is deposited first in the Kupfer cells, in hemochromatosis hemosiderin is first found in the liver parenchymal cells and periportal areas[10,13]. The regulation of iron absorption from the gastrointestinal tract is usually ascribed to a mucosal block. Cellular apoferritin has been implicated as the controlling factor for this block[11,12].

Since it is believed that storage iron in hemochromatosis may be utilized in the formation of hemoglobin, attempts at treatment have recently been directed toward the removal of iron by venesection[5,20]. However, this therapy is often not feasible in elderly patients who may have anemia. It appeared that chelating agents which have been used successfully in the treatment of lead poisoning might be employed similarly to remove iron deposits.

Chelating agents produce closely knit metal organic compounds which alter the physiological characteristics of the metal. Ethylenediamine tetraacetic acid (EDTA) is such a compound. It is a polyamino, polycarboxylic acid which is used in industry to inactivate

*Present address: 2275th U.S.A.F. Hospital, Beale Air Force Base, California.

trace metals, by combining them to form water soluble metal complexes or chelates. Lead[3,16] and iron[9,21] excretion have been enhanced clinically by the use of the di-sodium salt. New chelating agents have been produced which bind iron more effectively for some applications[6]. One of these agents N-Hydroxyethylethylenediamine triacetic acid (Versenol)* has been employed in the present study.

Versenol acid and its alkali metal salts are readily soluble in water and formation of metal chelates is complete at a pH of 7.0. Whereas ferric iron chelated with EDTA is decomposed in alkaline media to form ferric hydroxide, the ferric chelate of Versenol is stable under these conditions. Thus Versenol makes possible the chelation of ferric iron over a wider pH range. Studies in animals to date have shown decrease in calcium levels to be its only undesirable side effect. The structural formula of this agent is shown in Fig. 1.

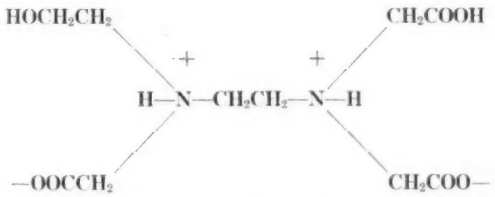


Fig. 1.—Structure of N-hydroxyethylethylenediamine triacetic acid, Versenol.

Method of Study. The Versenol solution was prepared in the following manner. One gram of Versenol acid was dissolved in 40 cc. of 0.9% saline. The solution was brought to pH 7.38 by the slow addition of dilute sodium hydroxide. Following filtration, it was autoclaved for 15 minutes at 15 pounds pressure.

No food was permitted prior to 9:00 A.M. of each day of the study. At that time blood samples were drawn, the intravenous infusion of normal saline solution with Versenol was started, and 24-hour urine collections begun. All containers, apparatus, and reagents used in the determinations were freed of iron by treatment with nitric acid followed by redistilled water. The method used for serum iron determination was that of Barkan and Walker[2] except that ascorbic acid was used as a reducing agent as suggested to one of the authors (J.G.R.) by Dr. Otto Schales. Application of this method to the serum of healthy individuals has given values averaging 125 micrograms per 100 cc. and ranging from 80 to 200 micrograms. Iron binding capacity of the serum was measured by the method of Ventura[19]. Iron was determined in the urine by applying the foregoing method to digests prepared according to a technique described in the Official Methods of the Association of Agricultural Chemists, 7th Ed., p. 105. Prothrombin time was determined by the method of Quick[15].

Case Histories and Results. CASE 1. E. L., a 69-year-old white male formerly employed as a head waiter, was admitted to Philadelphia General Hospital on April 17, 1953, with a history of progressive weakness and fatigue of 2 months' duration. Following an episode of pediculosis corporis several months prior to admission, he retained a brownish pigmentation of the skin. When seen in another hospital in March, 1953, areas of pigmentation on the soft palate were noticed. He admitted a moderate ingestion of alcohol over a period of 20 years but gave no history of previous transfusions and had no symptoms suggestive of diabetes mellitus. Physical examination revealed a brownish skin pigmentation, diffuse in the groin but spotty elsewhere. There were several small areas of dark brown pigmentation on the soft palate. The liver edge was smooth and palpable just below the costal margin.

Skin biopsy of the upper thigh showed hemosiderin. Liver biopsy showed deposits of hemosiderin in the periportal areas and evidence of early periportal fibrosis. Blood sugar and liver function tests were normal

*Kindly supplied by Bersworth Chemical Co., Framingham, Massachusetts.

except for bromsulfalein retention of 10%. Stool analysis showed an increase in free fat.

Twenty cubic centimeters of a solution of Versenol (0.5 gm.) were added to 100 cc. of 0.9% saline and administered intravenously over a one-hour period on each of 2 days. Urine specimens were collected from 9:00 A.M. to 9:00 A.M. on each of 3 control days prior to the administration of Versenol, during the 2 days of treatment, and for 3 days thereafter. The collections from each period were pooled and measured for volume and iron content. Fasting serum iron determinations were made preceding the first administration and on the first day following the treatment period.

TABLE 1.—ELECTROLYTE AND PROTHROMBIN DETERMINATIONS IN PATIENT WITH HEMOCHROMATOSIS GIVEN VERSENOL

		Blood					
Date	*Urine Fe mg./24 hrs.*	*Fe mcg./100 cc.*	*Per-cent saturation*	*Pro-thrombin time*	*Na*	*K*	*Ca*
1/ 7	1.89				143	6.0	10.2
1/ 8	2.62	144	100%		145	5.95	
1/ 9	2.67	144		88%			
*1/10	2.72						
*1/11	2.18	146		88%	144	4.2	10.2
*1/12	6.15	113		65%			
*1/13	10.50	93	100%	65%	141	5.7	9.6
1/14	6.28	141		65%	139	6.1	
1/15	6.61	119		65%	136	5.1	9.9
1/16	3.86						
1/20				65%	143	5.2	9.2

* Treatment period

In this patient the urinary iron excretion was within the normal range during the control period, 919 mcg. in 72 hours. During the treatment period this rose to 990 mcg. in 48 hours. Excretion in the posttreatment period was almost 1200 mcg. in 72 hours. The initial serum iron was 106 mcg. per 100 cc. with a serum iron binding protein saturation of 37.9%. On the first day of the posttreatment period the fasting serum iron level was 55 mcg. per 100 cc. with a saturation of 29%.

CASE 2. E. H., a 66-year-old white female, was admitted for the fourth time to the Philadelphia General Hospital on December 7, 1953. She had been in good health until the age of 38 when there had been an abrupt cessation of menses. At the age of 40, greyish brown pigmentation of the skin was noted. She was seen as an outpatient at Philadelphia General Hospital, in 1941, at the age of 54 because of weakness, fatigue, polyuria, and polydypsia; a diagnosis of diabetes mellitus was made. She was treated with globin insulin, 20 units morning and night. She was hospitalized, in 1942, because hepatomegaly was found, and a decrease in axillary and pubic hair noted. She admitted to an alcoholic intake of about one pint a day for 10 years, but claimed that food intake had been adequate during this period. She was discharged with a diagnosis of suspected hemochromatosis.

Her next hospital admission was in 1948, for an impacted fracture of the surgical neck of the left humerus. Physical findings were otherwise unchanged, and insulin requirements were the same.

Her third admission in September, 1950, was for the purpose of study. She was asymptomatic, and denied use of alcohol in the past 6 years. A skin biopsy showed deposits of hemosiderin. Liver function studies included negative cephalin and thymol flocculation tests, bilirubin of 1.13 mg., serum albumin of 5.3 gm., globulin of 2.5 gm. per 100 cc., and bromsulfalein retention of 39%. The cholesterol was 172 mg. per 100 cc. with 68% esters. The basal metabolic rate was +6 and there was a 70% drop in circulating eosinophils after injection of adrenalin.

Her final admission on December 7, 1953, was because of an intertrochanteric fracture of the right femur. She had no other complaints except for occasional dyspnea on exertion. Her weight had been stable in recent years.

A prominent finding was greyish-brown discoloration of the skin, most marked over ex-

posed areas. There was no mucosal pigmentation. The liver was palpable 3 fingerbreadths below the costal margin. Her right leg was in external rotation. The spleen was not felt. The insulin requirement had decreased in the past year and an attempt was made to demonstrate adrenal insufficiency.

Studies on admission included urine, blood count, and blood urea nitrogen measurements, all of which were within normal limits. Endocrine studies included a Kepler Power test with a value of 11. A glucose tolerance test was done and the fasting specimen found to show 173 mg. per 100 cc., one-half-hour specimen 184, one-hour specimen 209, two-hour specimen 222, three-hour specimen 242, four-hour specimen 262, and five-hour specimen 294 mg. per 100 cc. The output of 17-ketosteroids was 5.2 mg. The I^{131} uptake was 19%. The Thorn test showed an eosinophil drop from 155 to 65.

Hepatic and electrolyte studies gave the following results:

Cephalin flocculation	4+
Thymol turbidity	0.75 Maclagan units
Thymol flocculation	0
Bilirubin	1.98 mg./100 cc.
Chloride	94 mEq./L.
Protein	6.3 gm./100 cc.
Albumin	2.9 gm./100 cc.
Globulin	3.4 gm./100 cc.
Calcium	10.2 mg./100 cc.
Sodium	146 mEq./L.
Potassium	4.9 gm./100 cc.
Alkaline phosphatase	3.40 Bodansky units
Phosphorus	2.76 mg./100 cc.
Cholesterol	110 gm./100 cc.
Esters	64%
CO_2 capacity	22.6 mEq./L.

The serum iron was 140 mcg. per 100 cc. with the serum 100% saturated.

Liver biopsy showed marked periportal fibrosis and large amounts of hemosiderin in the parenchymal cells, and was reported as compatible with hemochromatosis.

The study consisted of a 3-day pre- and posttreatment period separated by a 4-day treatment phase. The patient was given 0.5 gm. of Versenol on January 10, 1954, and 1.0 gm. in 300 cc. of 1% saline over a one-hour period for the next 3 days.

Urinary iron excretion during the 3 days prior to treatment averaged 2.4 mg. daily. Excretion rose slightly to 2.7 mg. on the first day, and fell to 2.2 mg. on the second day of treatment. There was a marked rise on the third day of treatment to 6.15 mg. The peak of 10.5 mg. was reached on the fourth and last day of treatment. This increased iron excretion extended into the posttreatment period, being 6.28, 6.61, and 3.86 mg. respectively on succeeding days.

The serum iron first decreased on the third day of treatment to 113 mcg. per 100 cc. and reached a low of 93 mcg. per 100 cc. on the last day of treatment. On this day the saturation was still 100%. Liver function studies, blood urea nitrogen concentration and the hemoglobin were not appreciably altered as the result of treatment.

Except for a brief urinary tract infection, the patient did well until February 21, 1954, when she developed jaundice and a distended abdomen. She became disoriented and lethargic. A diagnosis of hepatic coma was made and treatment instituted. The course was rapidly downhill and the patient died on February 23, 1954. Necropsy was not permitted.

Discussion. It is doubtful whether the first patient had hemochromatosis even though liver and skin biopsies were compatible with the diagnosis. Normal serum iron values have been reported in hemochromatosis, but the finding of normal saturation is not consistent with this diagnosis. The 24-hour urinary excretion of iron rose to 445 mcg. with the use of Versenol during a 2-day collection period as opposed to a control of 306 mcg.

In the second patient, a classical and well proven case of hemochromatosis

with a serum level of 140 mcg. per 100 cc. and saturation of 100%, the response to Versenol therapy was more striking. The urinary iron excretion was increased more than fourfold by the fourth day of treatment. The enhanced iron excretion continued into the posttreatment period. On the third day of treatment, the serum iron dropped considerably. Despite a further drop on the fourth day, the serum iron saturation was still 100%. This observation is important suggesting that the process of hemoglobin regeneration, which depends on the availability of transport iron in the form of iron siderophyllin chelate, will not be disturbed by the depletion of iron stores through suitable chelate treatment. Liver function studies, blood urea nitrogen and electrolyte concentrations were not significantly affected. The prothrombin time, in contradistinction to the findings of Wishinsky *et al.*[21] with EDTA, was not altered significantly.

As there are approximately 2.65 gm. of iron in the circulating blood volume of 5 liters, it is evident that a much greater amount of iron is lost through the customary venesection of half a liter, that is, 265 mg., than was lost through a course of Versenol, namely, 16 mg. However, since phlebotomy may be contraindicated in certain stages of this disease, intermittent therapy of this type directed at reduction of nonhemoglobin iron stores in the body may be useful. Use of larger doses may be feasible since no toxic effects were noted in the 2 patients treated. If the chelating agent could be administered frequently and conveniently, this form of therapy should have distinct practical value. Chelating agents now available are apparently not effective by the oral route of administration[18], but studies in progress offer hope that this goal can be achieved.

Summary. 1. N-hydroxyethylethylenediamine triacetic acid (Versenol) was found to cause a marked increase of urinary excretion of iron in a patient suffering from hemochromatosis. Another patient with evidence of abnormal iron storage in the tissues showed a smaller increase in urinary iron excretion.

2. The increased iron excretion was sufficient to suggest that Versenol may have value for treatment of hemochromatosis. No untoward effects of the drug were noted.

REFERENCES

1. **Althausen, T. L., Doig, R. K., Weiden, S., Motteram, R., Turner, C. N.,** and **Moore, A.:** Arch. Int. Med., **88,** 553, 1951.
2. **Barkan, G.,** and **Walker, B. S.:** J. Biol. Chem., **135,** 37, 1940.
3. **Bessman, S. P., Reid, H.,** and **Rubin, M.:** Med. Ann. Dist. Columbia, **21,** 312, 1952.
4. **Butt, H. R.,** and **Wilder, R. M.:** Arch. Path., **26,** 262, 1938.
5. **Byers, H. R.,** and **Gitlow, S. E.:** Am. J. Clin. Path., **21,** 349, 1951.
6. **Chaberek, S., Jr.,** and **Bersworth, F. C.:** Science, **118,** 280, 1953.
7. **Chesner, C. J.:** J. Lab. & Clin. Med., **31,** 1029, 1946.
8. **Finch, C. A., Hegsted,, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S.,** and **Fluharty, R. G.:** Blood, **5,** 983, 1950.
9. **Figueroa, W. G., Adams, W. S., Bassett, S. H., Rosove, L.,** and **Davis, F.:** Am. J. Med., **17,** 101, 1954.
10. **Granick, S.:** Bull., New York Acad. Med., **25,** 403, 1949.
11. Idem: Science, **103,** 107, 1946.
12. **Hahn, P. F., Bale, W. F., Ross, J. F., Balfour, W. M.,** and **Whipple, G. H.:** J. Exp. Med., **78,** 169, 1943.

13. **Kleckner, M. S., Jr., Baggenstoss, A. H.,** and **Weir, J. F.:** Am. J. Med., **16,** 382, 1954.
14. **Lisa, J. R.,** and **Hart, J. F.:** New York State J. Med., **39,** 521, 1939.
15. **Quick, A. J.:** Hemorrhagic Disease and Physiology of Hemostasis. Springfield, Ill.: C. C Thomas, 1942.
16. **Rubin, M., Gignac, S., Bessman, S. P.,** and **Bolknap, E. L.:** Science, **117,** 659, 1953.
17. **Sheldon, J. H.:** Hemochromatosis. London: Oxford Univ. Press, 1935.
18. **Uhl, H.,** and **Rubin, M.:** Unpublished data.
19. **Ventura, S.:** J. Clin. Path., **5,** 271, 1952.
20. **Warthin, T. A., Peterson, E. W.,** and **Barr, J. H., Jr.:** Ann. Int. Med., **38,** 1066, 1953.
21. **Wishinsky, H., Weinberg, T., Prevost, E. M., Burgin, B.,** and **Miller, M. J.:** J. Lab. & Clin. Med., **42,** 550, 1953.

BINDINGS FOR COMPLETED VOLUMES

The desire to preserve the issues of THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES for permanent reference has brought numerous requests from subscribers for information as to how they may have their copies bound.

The Publishers' Authorized Binding Service, Box 776, Highland Park, Illinois, will bind your Journals carefully and economically. Write for details.

LACK OF EFFECT OF FAT INGESTION ON BLOOD COAGULATION

By Phil R. Manning, M.D.*

AND

Roy L. Walford, M.D.†

(From the Medical Service and the Laboratory Service, United States Air Force Hospital, Chanute Air Force Base, Illinois)

The observations of Strom and Jensen[6] indicate that there was a marked fall in the mortality from diseases of the circulatory system in Norway during the period 1943 to 1945. During this period restrictions caused by the war were such that the average diet decreased in caloric intake from 3400 to 2849 calories per day. The consumption of fat dropped from 159 to 71 gm. per day.

Another report from Norway by Dedichen *et al.*[1] stated that the incidence of postoperative thromboembolic phenomena decreased from about 16 per 1000 in 1941, to 6 per 1000 in 1944, and had increased to 21 per 1000 in 1948. It has been suggested that the decreased consumption of fat might affect the clotting mechanism of blood in such a way as to lessen the likelihood of thromboembolism.

Waldron, Beidelman, and Duncan[8] had previously reported that the oral ingestion of 60 cc. of 20% cream caused a 33.7% decrease in the clotting time of blood in the first half hour and a 43.7% decrease at the end of one hour.

The work of Tulloch *et al.*[7], however, failed to demonstrate that oral ingestion of the same amount of cream would alter the coagulation time. These workers suggested that Waldron, *et al.*, were able to demonstrate a change in the clotting time because they used one syringe for successive venipunctures. It was suggested that thrombin from the first venipuncture remained adhered to the syringe and shortened the succeeding clotting times.

More recently Fullerton *et al.*[4] found that the blood clotting time was accelerated in patients who had ingested a meal containing 85 gm. of fat. The greatest acceleration of the clotting time occurred 3 to 4 hours after ingestion of the fatty meal. This time relation is in keeping with the maximum increase in the blood lipids which occurs after a fatty meal[5]. Confirmation of this work would furnish at least a partial explanation for the observations which indicate that a fall in postoperative thromboembolic episodes might accompany a decrease in dietary fat.

Methods and Materials. INDUCTION OF LIPEMIA. Lipemia was induced by the oral administration of 240 cc. of 12%, 20% and 40% cream respectively to 3 groups of 4 patients each as indicated in Table 1. The cream was given in a fasting state, and is equivalent to 29, 48 and 96 gm. of fat. A butter-egg-bacon meal identical to that employed by Fullerton *et al.*[4], was given to 18 patients. The meal contains 85 gm. of fat.

*Formerly Assistant Chief of the Medical Services, USAF Hospital, Chanute Air Force Base, Illinois. Present Address: Department of Medicine, University of Southern California, Los Angeles 33, California.

†Formerly Chief of the Laboratory Service, USAF Hospital, Chanute Air Force Base, Illinois. Present Address: Department of Pathology, School of Medicine, University of California at Los Angeles, California.

Generally at each bleeding a tube of the patient's blood was set aside in order to observe the extent of gross lipemia.

COAGULATION TIME. Four to five cubic centimeters of blood were drawn into silicone-lined syringes with a #20 gauge needle. The needle was removed and 8 to 10 drops of blood were delivered into each of 2 silicone-lined new Kahn tubes. These tubes had been allowed to remain in a 38° C. water bath for a number of minutes. The tubes were immediately returned to the water bath. The first tube was examined for coagulation at the end of 10 minutes and at 2½-minute intervals thereafter. When this blood had clotted, the second tube was examined immediately and at intervals of 2½ minutes. The tubes were examined by gentle tilting. The endpoint was taken as the formation of a definite coagulum. In the great majority of cases, the tube could be completely inverted at this point without loss of blood. The average coagulation time of the 2 tubes was recorded as the final result. In 9 cases, after 4 to 5 cc. of blood had been drawn through a silicone-lined needle, the syringe was discarded and the drops of blood collected directly into the Kahn tubes. This variation in technique seemed to have no effect upon the results obtained. In all cases, if the initial venipuncture was poor, the needle and syringe were discarded and a new attempt made. In order to estimate roughly the technical variation of this method in our hands, one control individual was bled 5 times at one sitting. (In this small series the range [2σ] was 22 to 32 minutes.) All readings were reported to the nearest minute.

CLOT RETRACTION. This was determined according to the method outlined by L. W. Diggs[2].

PROTHROMBIN CONSUMPTION. This was determined according to a modification of Quick's method. (Frommeyer and Epstein[3]).

Results. Reference is made to Tables 1 and 2. We were unable to demonstrate that the ingestion of varying amounts and types of fat had any significant effect upon the rate of blood coagulation. The 3 groups of 4 patients each as listed in Table 1 and the 18 patients listed in Table 2 were analyzed separately by a statistical study of the between column variance.* The results were not significant on a 5% level. Also, analysis of Table 2 by the t-method showed no significant variation. The age of the patient did not appear to influence the results. In addition, the per cent of clot retraction and the prothrombin consumption times were not altered to any statistically significant degree by the ingestion of fat.

In general the ingestion of 12% cream was followed by a slight gross lipemia, the 20% cream by a moderate, and the 40% cream by a moderate to marked gross lipemia. The height of the gross lipemia was at a 3- to 4-hour interval.

Discussion. Our results agree with those of Tulloch *et al.*[7] in that we were unable to demonstrate that the ingestion of cream had any effect upon the speed of blood clotting. However, it

* Statistical methods:

(1) Analysis of between column variance

Table 2 is taken as example

a. square the individuals and add (Ans. 49,851)
b. obtain total for each column, square these totals, sum these squares, and divide this total by number of individuals in each column (Ans. 47,621)
c. total all individuals, square this, and divide by total number of individuals (Ans. 47,585)

Set up the following:

Source of Variance	*Sum of Squares*	*Degrees Freedom*	*Mean Squares*
Between column	(b)−(c)=36	(m−1)=2	19
Within column	(a)−(b)=2,230	m(n−1)=51	43

Ratio of larger mean square to smaller=43/19=2.26
Reference to tables reveals that for degrees freedom 2 and 51, $p>0.05$

(2) Comparison of column #1 with columns #2 and #3 respectively by the t-test reveals t values of 0.86 and 0.33 respectively. This has no significance on a 0.10 level.

TABLE 1.—EFFECT OF INGESTION OF 240 CC. CREAM ON CLOT RETRACTION, COAGULATION TIME, AND PROTHROMBIN CONSUMPTION

Patient	Age	% Cream	*% Clot Retraction					*Coagulation Time (min.)					*Prothrombin Consumption (sec.)					Prothrombin Control (sec.)	
																		100%	10%
1	20	12	41	39	42	46		28	22	27	26	24	50	60	65	70	60	14	42
2	20	12	37	39	42	37	43	27	25	26	32	22	63	50	45	49	49	14	42
3	22	12	49	48	53			22	23	20	22		128	121	87	112		17	106
4	21	12	34	33	35	30		26	29	31	25		100	203	87	151		17	106
5†	37	20	40	47	46	47		27	28	25	35	27	33	32	32	28	28	14	40
6	20	20	49	40		51	44	29	27	23	19	26	48	56	43	58	53	14	40
7	20	20		46	46	47	50	25	24	20	28	22	43	45	49	58	50	14	40
8	20	20	44	39	39	40	42	25	24	26	27	22	120	80	70	100	74	15	48
9	25	40	43	43	44	42	46	22	25	22	27	27	75	85	87	70	72	13	38
10	45	40		40		44	40	18	18	28	24	24	60	57	50	60	59	13	38
11	21	40	45	41	43	38	40	28	32	33	31	31	64	58	59	67	37	15	46
12	21	40	40	43	46	40	45	27	31	36	24	27	76	61	80	75	60	15	46

* From left to right: fasting, 1 hr., 2 hrs., 3 hrs., and 4 hrs., after ingestion of cream
† Indicates history of coronary occlusion

TABLE 2.—COAGULATION TIME IN MINUTES FASTING AND AFTER INGESTION OF BUTTER-EGG-BACON MEAL (85 GM. FAT)

Patient No.	*Age (years)*	*Clotting Time*		
		Fasting	*3 hrs.*	*4 hrs.*
1	18	25	28	23
2	19	25	30	36
3	20	32	23	27
4	22	41	33	31
5	23	33	32	30
6	23	16	16	22
7	29	24	31	27
8	31	31	24	29
9	34	28	27	33
10	43	27	27	26
11	48	31	37	32
12	49	47	34	29
13	53	37	24	31
14	54	33	37	38
15	55	25	28	28
16†	56	31	40	40
17	60	40	28	30
18	63	25	16	25

† Indicates history of coronary occlusion

may be noted that these workers used a relatively small amount of fat. Fullerton *et al.*[4] reported that 65 gm. and 85 gm. of fat decreased the blood clotting time, whereas 12 to 30 gm. in 8 of 9 cases had no effect. Nevertheless, with amounts of fat ranging from 29 to 96 gm. in the form of cream, and with a bacon-egg-butter meal containing 85 gm. of fat, we were unable to demonstrate any effect upon the clotting mechanism as measured by the coagulation time, clot retraction, and prothrombin consumption time.

Summary. The oral ingestion of varying amounts and types of fat caused no statistically significant change in the blood coagulation time, prothrombin consumption time, and clot retraction.

ACKNOWLEDGMENT: The authors are indebted to Professor John Henry, Department of Mechanical Engineering, University of Illinois, for advice in the statistical analyses employed.

REFERENCES

1. **Dedichen, J., Strom, A., Adelsten-Jensen, R.,** and **Closs, K.:** Transactions of the Fifth Conference on Factors Regulating Blood Pressure. New York: Josiah Macy, Jr. Foundation, p. 117, 1951.
2. **Diggs, L. W.:** A Textbook of Clinical Pathology, edited by S. E. Miller. 4th ed. Baltimore: Williams & Wilkins Co., 1952.
3. **Frommeyer, W. B.,** and **Epstein, R. D.:** Syllabus of Laboratory Examination in Clinical Diagnosis, edited by T. H. Haus. Cambridge: Harvard Univ. Press, 1952.
4. **Fullerton, H. W.,** and **Davie, W. J. A.:** Brit. Med. J., **2,** 250, 1953.
5. **Levy, E. S., Kraft, S. C.,** and **Necheles, H.:** J. Appl. Physiol., **4,** 848, 1952.
6. **Strom, A.,** and **Jensen, R. A.:** Lancet, **1,** 126, 1951.
7. **Tulloch, J. A., Overman, R. S.,** and **Wright, I. S.:** Am. J. Med., **14,** 674, 1953.
8. **Waldron, J. M., Beidelman, B.,** and **Duncan, G. G.:** Gastroenterology, **17,** 360, 1951.

CERTAIN OBSERVATIONS ON THE UPTAKE OF BASE IN UREMIA AND ACIDOSIS DUE TO ADVANCED RENAL DISEASE*

By Richard A. Neubauer, M.D.**
EXECUTIVE-DIRECTOR OF MEDICAL RESEARCH
WITH THE TECHNICAL ASSISTANCE OF
Elizabeth Garrigues, A.B.

(From the Medical Research Department, Memorial Hospital, Wilmington, Delaware)

The low-salt diet, a term frequently used synonymously with the low-sodium diet, has long been a part of the clinical armamentarium in the treatment of chronic renal disease[13]. Although salt restriction is beneficial in many instances, its potential dangers have been elucidated previously[3,10,22,23,44]. Patients with advanced renal disease frequently display an ability to maintain the integrity of the structure of the extracellular fluid with prolonged periods of salt restriction[36], and even with salt deprivation[34]. Thus the measurement of extracellular electrolytes may not in all instances reflect a disturbance of body base within the cell[8,27].

Recognition of a loss of body base in patients who are not the classic salt[26,47] or potassium losing nephritides[5,9,41] has previously been reported in the literature[6,7]. Elkinton[11], studying patients with chronic renal disease, showed that when sodium was used as bicarbonate, sodium definitely entered the cells when the chloride space was taken as being representative of the extracellular compartment. More recent studies by Nickel and his coworkers[34], using metabolic balance as well as exchangeable isotope techniques, demonstrated considerable intracellular cation deficiencies in 3 patients with known chronic renal disease. Yet in this latter series the depletion was not reflected in the extracellular electrolytes. Porter *et al.*[37] analyzing tissue electrolytes, alluded to a cell depletion of potassium in cases of renal failure again not reflected in serum studies.

Recent reports[28-32] have indicated the clinical and chemical changes occurring in patients suffering from uremia and acidosis with the administration of large doses of hypertonic sodium lactate, calcium and occasionally potassium salts. Maintenance therapy was used in most of these cases, and since this regimen is in some respects contrary to salt (sodium) restriction, data will be presented on 8 of these cases, most of whom initially showed varying degrees of base retention. The mechanisms by which the body depletion of base occurred will be postulated.

Materials and Methods. The 8 cases presented here were chosen for this study either because they were *in extremis* or because all other available measures of treatment for uremia and acidosis were unsuccessful. They were treated exactly according to a protocol published elsewhere[28] and received large doses of one or one-half molar sodium lactate orally or intravenously along with calcium salts (calcium lactate or gluconate) and

*This work was supported by a grant from the National Heart Institute, Bethesda, Maryland, the Delaware Heart Association, and funds made available by the Board of Directors of The Memorial Hospital, Wilmington, Delaware.

**Present address: Rolling Hill Hospital, Elkins Park, Pa.

frequently potassium salts (potassium chloride or potassium acetate). Four patients were comatose and the other 4 were ambulatory but experiencing severe signs and symptoms of uremia. In 6 cases the known renal disease had been recognized for from 2 to 17 years. The series comprised 5 cases of chronic glomerulonephritis, 2 cases of polycystic kidney disease and one case of chronic pyelonephritis.

On 2 ambulatory patients salt deprivation was used in the form of salt-free dextrimaltose for from 5 to 9 days. On one other patient a very low sodium diet was used. During the baseline period all of these patients who were not comatose were restricted as to protein intake, this being from 20 to 39 gm. daily along with forced calories[4,21].

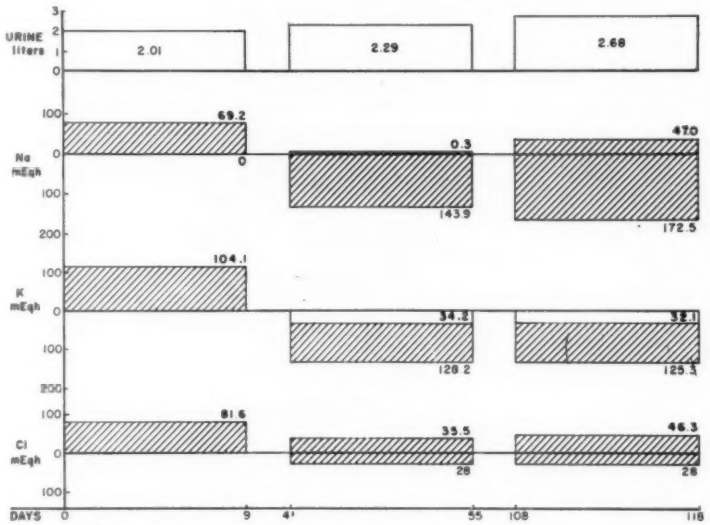


Fig. 1.—P.E.: During the first study period salt deprivation was accomplished with salt-free dextrimaltose. A negative sodium, potassium and chloride excretion occurred indicating inadequate conservative mechanisms. During this time there was no further azotemia or evidences of hypovolemia. After being at home for 32 days, where a 12.5 mEq. Na diet was prescribed but probably not accurately followed, a second study period was begun. Dietary Na remained at 12.5 mEq. and supplementary K of 36 mEq. per day was given. No retention of Na occurred but a slight K uptake was observed. During the third study period, again after a period at home, a negative sodium excretion occurred with the administration of 160 mEq. of 1 molar sodium lactate while on a 12.5 mEq. Na diet. Supplementary potassium of 30 mEq. daily was added. Along with the negative sodium excretion again some retention of potassium probably occurred.

The patients were studied as accurately as possible for the intake and output of sodium, potassium and chloride, either dietary or supplementary. The history was carefully reviewed as to previous treatment, symptoms of nausea and vomiting, recent fluid intake and diarrhea. When intravenous fluid was the only means of alimentation, the intake-output data could be calculated quite accurately, but when food was tolerated certain discrepancies occurred. Thus, in most instances, diets were weighed before and after serving in 3 of the 4 ambulatory cases. Calculations were made for sodium, potassium[2] and chloride, and to this the specially administered electrolytes were added in construction of the charts.

Daily blood determinations were done for blood urea nitrogen (reported elsewhere)[30] and for serum sodium, potassium, chloride and CO_2-combining power. Twenty-four hour urine samples were collected from 7 a.m. to 7 a.m., and measured and analyzed for sodium, potassium and chloride. Thus the concentration per liter and total excretion were known for the electrolytes mentioned. No correction for sweat or stool electrolytes was made, since the main interest at the time was the renal handling of these elements.

All patients were weighed daily when possible. Blood pressure and pulse were checked

2 to 4 times daily, but while receiving intravenous hypertonic sodium lactate, these were measured every 20 minutes during the infusion. Careful examinations for edema formation were made and these were correlated with the weight since space-volume determinations were unavailable at the time.

Sodium and potassium were determined on an internal standard flame photometer[14]. Chlorides, serum and urine, were measured according to the method of Schales and Schales[40]; CO_2-combining power was analyzed on a Van Slyke manometric apparatus[48]; while blood urea nitrogen was performed with the urease method[18].

Graphs were constructed following the method of Bassett[39]. The intake was plotted below the zero line and the output was plotted up from this. Thus a clear area below the zero line suggested a retention, while a shaded area above suggested a negative output. Therefore, the shaded area above or below the zero line gives the concentration per liter of the electrolytes as related to the urinary volume. Since discrepancies arise from dietary calculations when analyses of similar meals are not performed, average periods are recorded. By averaging the calculations for several days, the percentage of error may be reduced. It must be again emphasized that correction for stool and sweat was not made and thus this data may not be interpreted as absolute balance data. In certain cases the magnitude of change tends to override the error involved and allusions to retention may be made.

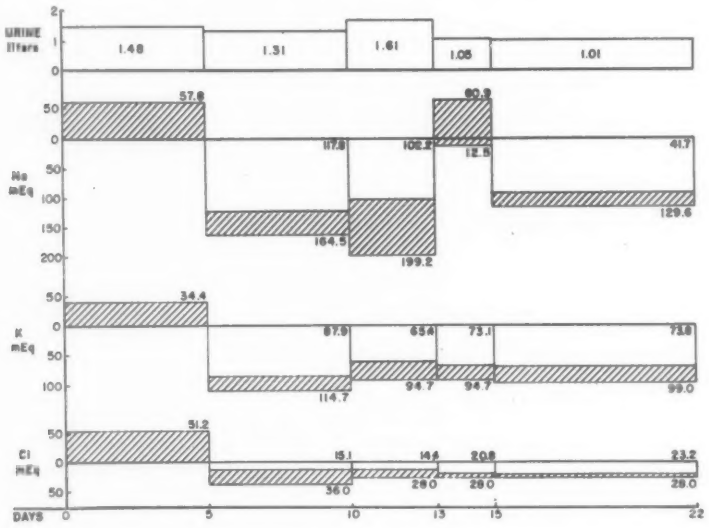


Fig. 2.—S. G.: Salt deprivation was used during the first period and another negative sodium chloride and potassium excretion was noted. In the second and third periods dietary sodium was 12.5 mEq. daily and supplementary 1 molar sodium lactate was given. Dietary K content during these periods amounted to 95 mEq. daily. Uptake of base during these periods may have in part been due to the previous period of loss. In the next 2 periods a low Na and 95 mEq. K diet were utilized. Potassium uptake continued but sodium conservation mechanisms were incomplete from 13 to 15 days. In the last period with supplemental sodium lactate, a moderate sodium retention occurred along with K retention.

Results. Table 1 presents each case with attention to potential mechanisms whereby a deficit of body base may occur. All patients had either continuous or intermittent vomiting for varying periods of time. Diarrhea occurred in only one case. In all cases except P.E., J.M., and A.H. therapy initially was intravenous. Dehydration clinically was corrected with the usual fluid

therapy before the administration of the *combined regimen*. These fluids in most cases included physiological saline, one-half physiological saline, potassium chloride, 1/6 molar sodium lactate, 5% glucose in water and 10% invert sugar.

Graphs representing P.E., S.G., and L.M. indicate that during sodium deprivation or restriction a negative sodium balance may occur. Yet under these circumstances there was no alteration in the chemical structure of the extracellular fluid or rise in the blood urea nitrogen during the study periods[22].

Following salt deprivation and then electrolyte administration S. G. apparently retained both sodium and potassium while P.E. apparently retained no sodium and practically no potassium. J. M. while on salt restriction may have compensated to some degree by retaining potassium, but no sodium was subsequently retained until the fourth study period. It is important to note that during the long intervals between study periods two of these patients were at home and absolute diet data were not available. Therefore, perhaps salt was ingested at home in sufficient quantities to explain the lack of retention.

Patient T.H. had 2+ clinical edema. It is of note that with the administration of hypertonic sodium lactate and with the retention of about 1000 mEq. of sodium in an 8-day period, there was a complete disappearance of edema fluid with no diuresis. This suggested

TABLE 1

Patient	*Age*	*Diagnosis*	*Known duration*	*Salt restriction*	*Nausea and vomiting*	*Admission dehydration*
J. M.	29	Chronic glomerulonephritis	5 years	Yes, intermittently 5 years	1 week	Mild. Clinically corrected before study
S. G.	31	Chronic glomerulonephritis	5 years	Yes, intermittently 5 years	6 weeks	Moderate. Clinically corrected before study
P. E.	27	Chronic glomerulonephritis	5 years	Yes, intermittently 5 years	4 weeks	Mild. Clinically corrected before study
L. S.	65	Chronic glomerulonephritis	3 weeks	None	3 weeks	Severe. Clinically partially corrected before study
B. O. N.	33	Chronic glomerulonephritis	3 weeks	None	3 weeks Diarrhea 3 days	Severe. Clinically corrected before study
M. Y.	56	Polycystic kidney	17 years	Yes, intermittently 3 years	6 weeks	Mild. Clinically corrected before study
A. H.	43	Polycystic kidney	2 years	Yes, intermittently 2 years	Intermittent 2 years	Slight. Clinically corrected before study
H. DeK.	56	Chronic pyelonephritis	9 months	None	Intermittent 9 months	Severe. Clinically corrected before study

that the volume of distribution of hypertonic sodium lactate must have been greater than the extracellular compartment as has been noted with sodium bicarbonate[42]. This patient appeared to retain base for a 27-day period. During the periods of supplemental potassium administration this patient sustained an elevated serum potassium but despite an order for the discontinuance of this acidosis had been excluded, the possibility of renal acidosis was considered and combined electrolyte therapy was begun within a period of 36 hours after water and salt hydration had been attempted. It is interesting that some uptake of sodium could be related to an expansion of the extracellular compartment but the negative chloride excretion makes this dubious in spite of

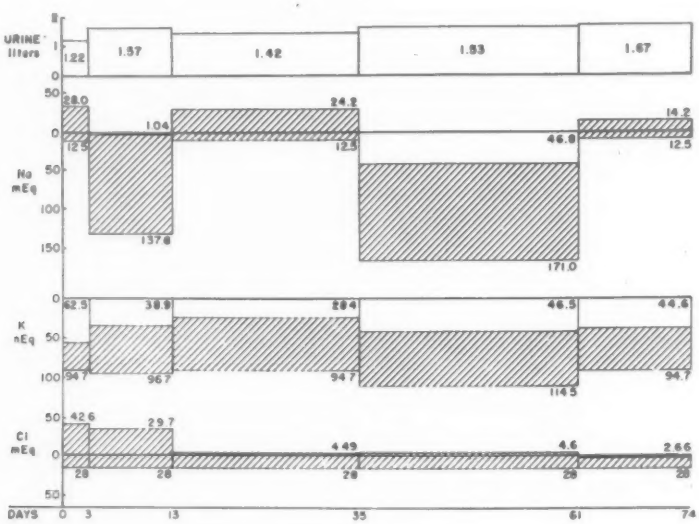


Fig. 3.—J.M.: A 12.5 mEq. Na, 95 mEq. K diet was used throughout the study. Some potassium retention was noted throughout the entire observation time. Without added sodium lactate negative sodium balances occurred but apparently diminished in concentration throughout the study. The effect of replacement of a possible body base deficit upon tubular mechanisms is not known.

ion the same dose was continued intravenously. When the serum potassium was noted to be above 7 mEq./L., intensive therapy with hypertonic glucose, calcium, and insulin was employed[1,25]. This was felt to be beneficial for under this regimen in spite of the additional potassium the serum value promptly returned to normal.

L.S., who was admitted to the hospital *in extremis* after having been found comatose in her room, was in severe clinical acidosis. After diabetic a fall in the serum chloride value. Further base uptake was not even suggested until the third period when apparently slight amounts of sodium and potassium were retained. This patient has served as her own control on 3 occasions when discontinuance of supplementary electrolytes has resulted in hospitalization for recurrence of uremic signs and symptoms. (Necropsy performed revealed far advanced chronic glomerulonephritis.)

Patient M.Y. was admitted to the

hospital for the 17th time in 16 years with uremia arising from polycystic kidney disease. The patient was treated for 2 weeks with isotonic intravenous fluids, including 1/6 molar sodium lactate[49] with no favorable clinical or chemical response. With the administration of hypertonic sodium lactate and added potassium, there was no uptake of base until after the sixth day when clinical improvement was obvious. The observed potassium retention may have reflected a better state of nutrition, and the initial chloride retention is difficult to explain since no clinical edema or weight gain was observed[45].

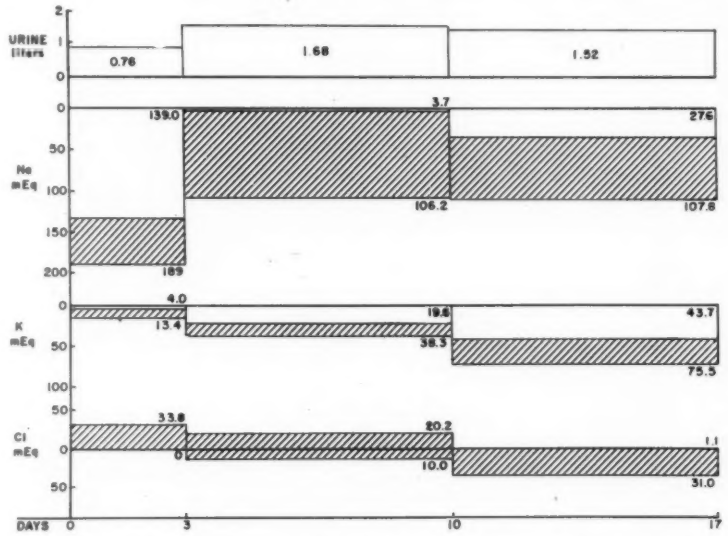


Fig. 4.—L.S.: Admitted *in extremis*, this patient had the shortest baseline data accrued and supplementary sodium lactate was begun within 48 hours. The initial uptake of sodium could be related to a re-expansion of the extracellular level but this is difficult to reconcile in view of the negative chloride excretion with a falling serum Cl level. Na equilibrium was approached in the second period but some retention of base occurred during the entire study. For the first 10 days all therapy with intravenous. Dietary Na from the 10th to 17th day was less than 10 mEq. and dietary K was 30 mEq. daily.

A.H. for 2 years prior to the electrolyte therapy had been maintained on three 1000 cc. intravenous infusions of 1/6 molar sodium lactate and 500 cc. of blood each week. It is of interest that with oral hypertonic electrolyte solutions he initially retained both sodium and potassium. During this time he required no further intravenous therapy and was completely rehabilitated for a period of 6 months with only one transfusion during that time. (Necropsy displayed polycystic kidneys weighing 4000 gm. each.)

H.D.K. who had a 9-month history of nausea and vomiting had been treated previously for 2 weeks with isotonic and hypotonic solutions of saline and potassium with no clinical or chemical improvement. With the institution of the combined electrolyte regimen his blood urea fell 85 mg. per 100 cc. in a 24-hour period in spite of a urea clearance of only 6% of normal. From the history a large cell cation deficit would have been suspected, but from the intake-output data practically no

base was retained. Perhaps the isotonic solutions administered previous to the hypertonic solutions furnished adequate base. The explanation of a negative sodium and potassium along with a negative chloride excretion is not obvious.

Discussion. Although these metabolic studies are subject to some degree of error, the changes observed appear to suggest that most of these cases in the series had some body deficit of base which was not reflected in the serum sodium and potassium values. Sunderman[46] has demonstrated that the osmolarity of the extracellular fluid may be maintained or elevated until death in patients with chronic renal disease and it has been suggested that the retention of blood urea and other osmotically active materials may be a homostatic mechanism in the preservation of the structure of the extracellular fluid.

The administration of added electrolytes had very little effect on the serum sodium values, but in all instances when potassium was not added initially, a decrease in the serum potassium value occurred. This was corrected either by adding potassium as acetate or chloride, or by an improvement in the patient's nutrition.

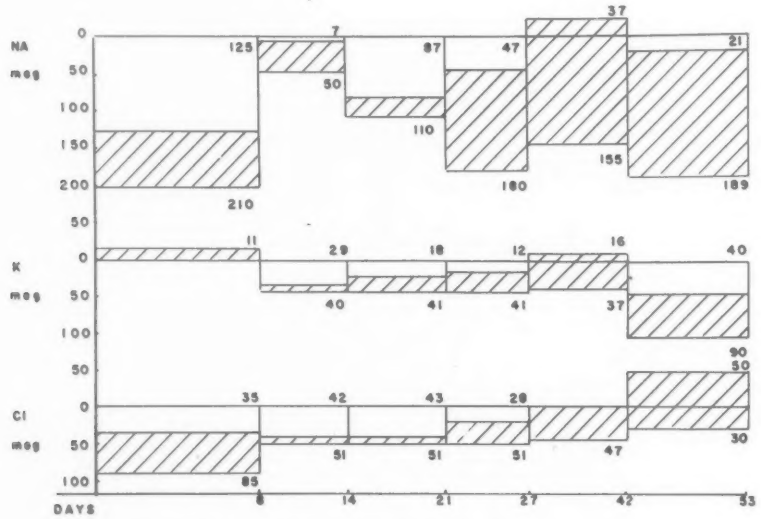


Fig. 5.—B.O.N.: During the first 5 days regular dextrimaltose (85 mEq. NaCl) was given daily in addition to intravenous sodium lactate. After the 5th day supplementary K was administered, and the patient apparently retained base for 27 days. The negative excretions during days 27 to 42 are difficult to explain in view of further retention in the last period. It is of note that this patient lost edema fluid during the first period while retaining sodium indicating a larger volume of distribution than the extracellular compartment. Only total excretions were calculated in this case and thus urinary volumes are not recorded.

The CO_2-combining power rose above normal values in all cases with a concomitant drop in the extracellular chloride level. The serum electrolyte determinations, therefore, were of little value either in alluding to a body base deficit initially or, with the exception of potassium, in directing treatment toward a deficiency.

In this series, one patient was edematous and edema fluid completely

disappeared while receiving sodium. None of the other cases while on therapy manifested edema or had weight gains that could not be explained on the basis of improved nutritional status.

Although space volume measurements were not available, it appeared that the volume of distribution of hypertonic sodium lactate was greater than the extracellular fluid. This is in this again indicating the probability of an intracellular migration of sodium, or the ability of the damaged kidney to handle this ion.

At the time of electrolyte study the degree of uptake of base was not associated with the clinical condition of the patient nor could it be closely related to the history. Four patients had previously been on sodium restriction

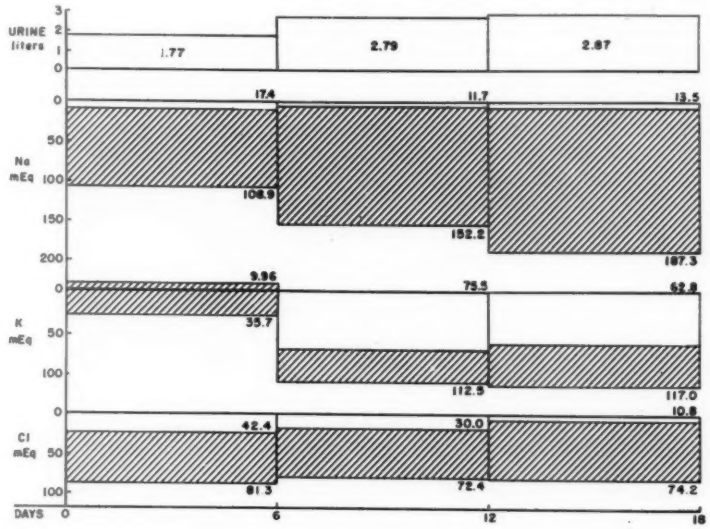


Fig. 6.—M.Y.: This comatose patient had been on complete parenteral maintenance for 10 days prior to the study. Only isotonic fluids had been used, but negligible sodium retention occurred, and when corrected for stool and skin, near Na equilibrium existed for the next 18 days. For the first period, all maintenance was intravenous. During the next 2 periods, dietary K was 60 and 76 mEq. daily. Additional salt (34 mEq. Na) was given to this patient during the last 2 periods because of a very low extracellular chloride value. With clinical improvement and better nutrition, this patient retained potassium during the last 12 days.

keeping with Singer's experience with sodium bicarbonate where he was able to show that the probable volume of distribution of sodium as bicarbonate was about five-sevenths of the body weight[42]. No hypertension was induced with the administration of sodium to this group of patients; nor was there any aggravation of an existing hypertension. No patient developed acute pulmonary edema or peripheral edema, for periods of from 2 to 5 years. All patients prior to therapy had been vomiting intermittently for periods of from 2 weeks to 9 months. Only one patient had diarrhea, but all patients had upon admission varying degrees of dehydration. It must be emphasized that before the *combined electrolyte regimen* was used, clinical dehydration was overcome with the conventional fluid replacement. Thus the base uptakes

demonstrated occurred after the usual therapy, with the exception of patient L. S., who was *in extremis*. Therefore, it appeared in this small series that the use of isotonic fluids in amounts sufficient to overcome clinical dehydration did not always furnish adequate body base.

Initially all patients had had periods of progressive weight loss that were well correlated with duration of nausea and vomiting. Fluid intake varied in the cases, and prior to conventional therapy or electrolyte management, the history did not seem to indicate that fluid intake was 1000 cc. above the urinary output. Added water in conventional concept of 1000 cc. for metabolic purposes probably was not available[15].

It is interesting in 3 patients where salt restriction or salt deprivation was used, that the urinary output of sodium was greater than the intake. This may be explained by inadequate conservation mechanisms. The recent work does indicate that such mechanisms are still inherent in advanced renal disease[34,35]. The loss of sodium via the kidney by salt restriction was pointed out by Newburgh in 1948[33]. He foresaw difficulties at that time even though the negative balance amounted to only a few milliequivalents daily. This multiplied by weeks or years could produce a tremendous depletion of cation.

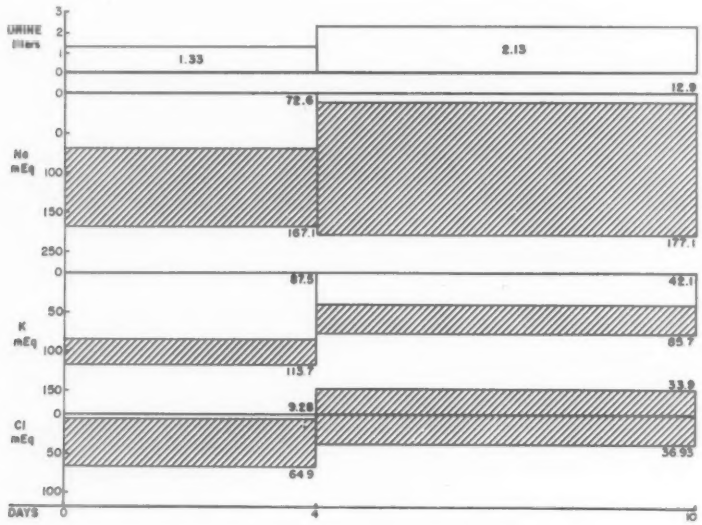


Fig. 7.—A.H.: A.H. had been on a 5-gm. salt diet and had received 2000 cc. of 1/6 M Na lactate and 500 cc. of blood weekly for 2 years prior to the study. Dietary Na accounted for 17 mEq. daily and dietary K 77 mEq. The major uptake of base was associated with K.

Renal acidosis is known to account for a body loss of sodium, potassium, calcium and magnesium[16]. When the ammonium-forming mechanism of the kidney is unable to keep up with the excretion of anion, fixed base is then lost. It is believed that the above features probably accounted for the body loss of base in these patients.

Although in several instances sodium was retained initially, long-term studies suggest that these amounts of sodium are eventually recovered. Although

metabolic data is not available, a hypothesis may be that with improved nutritional status the cell uptake of sodium which appeared to be an emergency was eventually exchanged for dietary potassium; this being the main physiologic cation of the cell[15].

In this series there was no electrolyte correction for stool, sweat, or for one instance of diarrhea. The main interest at the time was the renal handling of electrolytes. It was seen in all cases studied that regardless of the baseline urinary sodium concentration per liter, with the administration of hypertonic sodium lactate the concentration of sodium in urine rose at times to almost normal levels, regardless of the degree of kidney pathology. The effect of electrolyte therapy along with protein restriction on reduction of renal osmotic work is not known, but according to Newburgh's calculations this may be a feature in reducing renal energy where so little reserve is available[33]. When sodium was administered with lactate it appeared that the excretion of sodium was intimately related to this anion.

Toxic metabolites and retention products important in uremia continue to be sought, but the possibility of a more fundamental role of the concomitant base deficit in causing disability exists. Attempts at correction of the deficit appear logical then, despite certain inherent difficulties. Although potassium is important among the deficient cations, the dangers of administering large amounts of base as potassium are well known[12,17,19,24,38,43]. Sodium is most often administered with a strong non-metabolizable anion which demands excretion, displacement of bicarbonate, or dilution of extracellular fluid. Administration with lactate[20] may

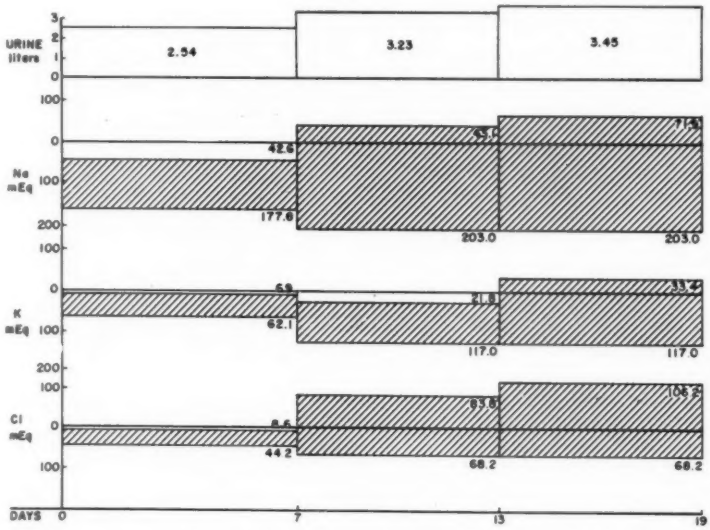


Fig. 8.—H.DeK.: Three weeks prior to the intake-output study, this patient had been on parenteral maintenance with isotonic fluids. Although this patient had been vomiting intermittently for 9 months, the isotonic fluid therapy apparently corrected the body deficit of base that may have been present. Practically no base was retained in this case and the negative sodium excretions were not correlated with a clearance of edema fluid.

be advantageous on this account, as base may be made available for neutralization of acid metabolites in the body fluids and in excretion via the kidney in which normal acidification and ammonium forming mechanisms are deficient. That relatively exact homeostatic regulation may be achieved in this manner by kidneys that are seriously impaired would be consistent with Platt's postulate that remaining nephrons may be capable of functioning in a supernormal manner[36].

Summary. 1. Eight cases of advanced renal failure were reviewed as to potential mechanisms which would produce a body deficit of base.

2. Intake-output data for sodium, potassium and chloride is presented during the administration of supplementary electrolytes.

3. Most of the cases studied appeared to have varying degrees of body base deficit.

4. The history or clinical condition of the patient did not present a reliable guide to the magnitude of cation depletion at the time of the metabolic study. The role of isotonic fluids was noted.

5. When sodium was administered as hypertonic sodium lactate to these cases the excretion of sodium in the urine appeared to be intimately related to the anion.

REFERENCES

1. **Beall, D., Bywaters, E. G. L., Bestey, R. N. R.,** and **Miles, J. A. R.:** Brit. Med. J., **1,** 432, 1941.
2. **Bills, C. E., McDonald, F. G., Neidermeier, W.,** and **Schwarts, M. C.:** J. Am. Dietet. Assn., **25,** 304, 1949.
3. **Blum, L., Graber, P.,** and **Caulaert, V.:** Ann. de Med., **25,** 34, 1929.
4. **Borst, J. G. G.:** Lancet, **1,** 824, 1949.
5. **Brown, M. R., Currens, J. A.,** and **Marchland, J. F.:** J. Am. Med. Assn., **124,** 545, 1944.
6. **Bywaters, E. G. L.:** Ibid., **124,** 1103, 1944.
7. **Bywaters, E. G. L.,** and **Stead, J. F.:** Clin. Sci., **5,** 195, 1945.
8. **Darrow, D. C.:** J. Ped., **28,** 515, 1946.
9. **Earle, D. P., Sherry, S., Eichna, L. W.,** and **Conan, D. J.:** Am. J. Med., **11,** 283, 1951.
10. **Elkinton, J. R., Danowski, T. S.,** and **Winkler, A. W.:** J. Clin. Invest., **25,** 120, 1946.
11. **Elkinton, J. R., Squires, R. D.,** and **Singer, R. B.:** Ibid., **30,** 381, 1951.
12. **Finch, C. A.,** and **Marchland, J. F.:** Am. J. Med. Sci., **206,** 507, 1943.
13. **Fishberg, A. M.:** Hypertension and Nephritis. 3rd ed., Philadelphia: Lea & Febiger, 1934, p. 164.
14. **Fox, C. L., Jr.:** Anal. Chem., **23,** 137, 1951.
15. **Gamble, J. L.:** Chemical Anatomy, Physiology, and Pathology of the Extracellular Fluid: A Lecture Syllabus. Cambridge: Harvard Univ. Press, 1947, p. 159.
16. **Gamble, J. L., Blackfan, K. D.,** and **Hamilton, B.:** J. Clin. Invest., **1,** 359, 1925.
17. **Hollander, G.,** and **Kissin, B.:** Med. Rev., **162,** 16, 1949.
18. **Karr, W. G.:** J. Lab. & Clin. Med., **9,** 329, 1924.
19. **Keith, N. M., Burchell, H. B.,** and **Baggenstoss, A.:** Am. J. Med. Sci., **217,** 1, 1944.
20. **Krebs, H. A.:** Harvey Lectures, Series 64, New York, 1948-49.
21. **Kolff, W. J.:** Am. J. Med., **12,** 667, 1952.
22. **Landis, E. M., Elsom, K. A., Bolt, P. A.,** and **Shiels, E.:** J. Clin. Invest., **14,** 525, 1935.
23. **McCance, R. A.:** Proc. Royal Soc. London, Series B, **119,** 245, 1936.
24. **Marchland, J. F.,** and **Finch, C. A.:** Arch. Int. Med., **73,** 384, 1944.
25. **Merrill, J. P., Levine, H. D., Somerville, W.,** and **Smith, S.:** Ann. Int. Med., **33,** 797, 1950.
26. **Murphy, F. D., Settimi, A. L.,** and **Kozokoff, N. J.:** Ibid., **38,** 1160, 1953.
27. **Nadler, C. S., Bellet, S., Reinhold, J. G.,** and **Lanning, M.:** Am. J. Med. Sci., **218,** 308, 1949.
28. **Neubauer, R. A.:** Ibid., **227,** 628, 1954.

29. Idem: Delaware State Med. J., **24**, 97, 1952.
30. **Neubauer, R. A.**, and **Dunsmore, L.**: Ibid., **25**, 283, 1953.
31. Iidem: J. Urol., in press.
32. **Neubauer, R. A.**, and **Porter, R. R.**: Clin. Res. Proc., **1**, 58, 1953.
33. **Newburgh, L. H.**: Bull. New York Acad. Med., **24**, 137, 1948.
34. **Nickel, J. F., Lawrence, P. B., Leifer, E.**, and **Bradley, S. E.**: J Clin. Invest., **32**, 137, 1948.
35. **Platt, R.**: Clin. Sci., **9**, 367, 1950.
36. Idem: Lancet, **1**, 1239, 1951.
37. **Porter, R. R., Neubauer, R. A., Fischer, E.**, and **Young, N.**: Tr. Am. Clin. & Climatol. Assn., **62**, 239, 1951.
38. **Rabinowitch, I. M.**: J. Biol. Chem., **62**, 667, 1924.
39. **Reifenstein, E. C., Jr., Albright, F.**, and **Wells, S. L.**: J. Clin. Endocrinol., **5**, 367, 1945.
40. **Schales, O.**, and **Schales, S. S.**: J. Biol. Chem., **140**, 897, 1941.
41. **Sherry, S., Eichna, L. W.**, and **Earle, D. P.**: J. Clin. Invest., **27**, 557, 1948.
42. **Singer, R. B., Clark, J. K., Crosby, A. P., Jr.**, and **Barker, E. S.**: Fed. Proc., **11**, 148, 1952.
43. **Smillie, W. G.**: Arch. Int. Med., **16**, 330, 1915.
44. **Soloff, L. A.**, and **Zatuchni, J.**: J. Am. Med. Assn., **139**, 1136, 1949.
45. **Steele, J. M.**: Bull. New York Acad. Med., **27**, 679, 1951.
46. **Sunderman, F. W.**: New York State J. Med., **53**, 57, 1953.
47. **Thorn, G. W., Koepf, G. F.**, and **Clinton, M., Jr.**: New England J. Med., **231**, 76, 1944.
48. **Van Slyke, D. D.**, and **Neill, J. M.**: J. Biol. Chem., **61**, 523, 1924.
49. **Yeoman, A.**, and **Stueck, G. M., Jr.**: Am. J. Med., **13**, 183, 1952.

STUDIES OF THYROID FUNCTION IN MYOTONIA DYSTROPHICA*

By C. E. Benda, M.D.
DIRECTOR OF RESEARCH AND CLINICAL PSYCHIATRY, W. E. FERNALD STATE SCHOOL, WAVERLEY, MASSACHUSETTS; INSTRUCTOR, HARVARD MEDICAL SCHOOL; LECTURER, TUFTS MEDICAL SCHOOL

C. J. Maletskos, Ph.D.
RESEARCH ASSOCIATE

J. C. Hutchinson, M.D.
RESEARCH ASSISTANT

AND

E. B. Thomas, S.M.
RESEARCH ASSISTANT
RADIOACTIVITY CENTER, DEPARTMENT OF PHYSICS, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, MASSACHUSETTS

Myotonia dystrophica is a genetic neuro-endocrine disorder in which a specific myotonic reaction of striated muscles is associated with progressive muscular dystrophy and complex endocrine disorders in which gonadal atrophy, both in males and females, is most characteristic. Extensive clinical and endocrine studies which will be reported elsewhere** indicate that, in addition to the gonadal atrophy, changes in the pituitary of the type of basophilism, anomalies in the adrenals and thyroid pathology were observed. Four necropsies which were available to us, and a survey of the literature, indicate that myotonia dystrophica is usually associated with a resting colloid goiter. The thyroids in our cases weighed 37, 75, 22½, and 30 gm., respectively, in contrast to a control material of over 300 cases of other types of neuropathological conditions excepting goiter, in which hardly a single thyroid weighed more than 25 gm. These observations suggested that it might be desirable to study the thyroid function in myotonic patients with the use of radioactive iodine and determinations of protein-bound iodine.

Method. Each of 6 male patients was administered (approximately 3 to 4 hours after breakfast) a tracer dose of 54 μc I^{131} in 100 cc. of water containing 100γ I^{127} carrier. The drinking glass was washed with 100 cc. of water, making a total of 200 cc. of water consumed during the administration of I^{131}. Two 24-hour urine collections were made under constant surveillance. During this period the patients were kept in bed on their normal diet. No previous iodine therapy had been administered to these patients.

The *in vivo* uptake by the thyroid was determined on the 1st, 2nd, 3rd, 6th and 8th days after administration. These measurements were carried out on a 4-channel scintillation counter†[7] located in the Thyroid

*This work was supported in part by the U. S. Atomic Energy Commission under Contract AT(30-1)-952.

**To be published in Medicine.

†Four detectors (using NaI[T] crystals) located symmetrically, in a horizontal plane, around the neck. A model based on this original design has been described briefly by Brownell and Stanbury[3]. The equipment had a sensitivity of approximately 1100‡ cpm/μc I^{131} and a background of approximately 1000 cpm.

‡Cpm = (Geiger) Counts per minute; μc = microcurie.

Laboratory of the Beth Israel Hospital, Boston, Mass.* Corrections for absorption and scattering of the I^{131} γ-rays by each patient were made by placing an I^{131} source (held in a small thin rubber container) on the anterior surface of the neck just below the cricoid cartilage. The reference standard was an I^{131} source (equal in activity to the doses) in 100 cc. of water contained in a 100-cc. volumetric flask. The error in the absolute value of the uptake can be as large as $\pm$ 10%, depending on the body build and thyroid function of the patient. It will be seen from the recovery data that the error in the absolute value of the uptake for these patients is small. The error in the relative values of the uptakes for each individual has a standard deviation equal to approximately 2 to 3% as determined by a series of measurements in which subjects were removed from and reseated in the equipment. The urine activity was measured with the same instrument on the individual daily urine output, contained in 2 1-liter jars. No corrections were necessary for the urine determinations. The standard deviation of the urine measurements is approximately 2 to 3%.

Protein bound iodine (PBI) measurements† were made on 4 of the patients 7 days before the I^{131} administration and on all the patients 3 days after. Aliquots of the distillate used to measure the PBI on the 3rd day after the dose were obtained to determine the organically bound I^{131} level in the circulation (PBI^{131}). The iodine was precipitated as AgI by adding 5 drops 1 : 1 HNO_3, 8 drops 5 mg./cc. NaI solution and 7 drops saturated $AgNO_3$ solution to 15 cc. of the distillate. The solution was shaken to coagulate the AgI and was allowed to stand for one hour. The solution was filtered on a two-section sintered glass funnel and the AgI precipitate was recovered as a flat disc on filter paper. Control samples of I^{131} were made in the same manner, and all samples were counted with an end-window β-ray counter on automatic counting equipment designed and built at the Massachusetts Institute of Technology. Background was 30 cpm. The standard deviation of the PBI^{131} measurements is approximately 25%. The PBI residue material of the 3rd day was counted with a scintillation counter to estimate the inorganic I^{131} content of the serum. These measurements were not as good as would be desirable, because of the low counting rate to background ratio, but it was possible to set an upper limit to the serum inorganic I^{131} values.

Results. The results of the measurements on the 6 patients are presented in Tables 1 and 2.

It can be seen that the values of thyroid uptake (15 to 42% dose) and urinary output (55 to 70% dose for the 1st day and 3 to 10% dose for the 2nd day) (Table 1) lie in the range of normal thyroid function. The recovery of the administered activity on the 2nd day is good (average recovery = 97%.). From the data in Table 2 the total circulating I^{131} is less than 5% of the dose. Thus the recovery of the activity administered is satisfactory.

The thyroid uptake is almost constant over the 8-day observation period. The biological half-lives of the I^{131} in the thyroids of these patients range from 100 to 360 days and average approximately 240 days. While it is not correct to determine a biological half-life from such short term measurements (both from the point of view of accuracy and from considerations of the dynamics of the system[9]), the data do lead to the conclusion that the biological half-lives are long. This is further evidence, based on the findings of Burns *et al.*[4], that the thyroid function of these patients is normal. A probability does exist, however, that the biological half-lives for these patients is greater than for normals.

The PBI values (Table 2) for both periods of analysis are within the normal range. There is no significant difference between the group of four, 7 days before the I^{131} administration and the same four or the whole group, 3 days after. The PBI values range from 33 to 65γI/1 serum and average 50γI/1 serum.

*The courtesy of Dr. A. Stone Freeberg and Dr. G. Kurland is gratefully acknowledged.

†These measurements were carried out by Mrs. Dorothy E. Pratt of the Massachusetts General Hospital, Boston, Massachusetts.

The choice of the 3rd day after the administration of the dose for the PBI^{131} measurements was a best estimate, from the results of McConahey *et al.*[8] and Brownell[1], of the time at which the PBI^{131} values would be a maximum. The data of Freedberg *et al.*[5] suggest that one day is an appropriate time and they indicate that values on the 2nd and 3rd days increase irregularly from the 1st day values. It would seem that the PBI^{131} levels are probably not rapidly varying values between the 1st and 4th days after administration of the dose, although the available information does not permit a definite conclusion to this effect. The choice of the 3rd day is also a time which is closer to the time at which equilibrium is established between the specific activities of all the iodine compartments of the body. By using PBI^{131} values of this time, therefore, a more accurate calculation of the organic iodine content of the thyroid can be made.*

TABLE 1.—PER CENT THYROID UPTAKE AND URINARY EXCRETION AND PER CENT RECOVERY FOLLOWING A 54 μc DOSE OF I^{131}

	Days after Administration								
	1	*2*	*3*	*6*	*8*	*1*	*2*	*1*	*2*
	Uptake					*Excretion*		*Recovery*	
Patient									
JD	24.7	23.8	24.4	23.7	23.7	60.4	7.5	85.1	91.7
FD	15.7	15.3	14.9	15.0	14.6	69.6	10.3	85.3	95.2
SD	37.3	36.6	36.4	38.6	36.1	58.2	2.7	95.5	97.5
HH	36.3	39.4	36.9	37.9	37.5	54.9	3.2	91.2	97.5
AL	42.1	42.0	37.2	38.4	39.4	57.8	3.2	99.9	103.0
HW	20.3	19.6	20.2	19.2	19.4	69.1	7.5	89.4	96.2
Average	29.4	29.5	28.3	28.8	28.5	61.7	5.7	91.1	96.9

TABLE 2.—PROTEIN BOUND IODINE (PBI), RADIOACTIVE PROTEIN BOUND IODINE (PBI^{131}) AND THYROID ORGANIC IODINE CONTENT

	PBI (γI/l Serum)		*PBI^{131} (3 Days After)*		
Patient	*7 Days Before*	*3 Days After*	*Per Cent Dose/l serum*	*Per Cent Dose in Extra-thyroidal Tissues**	*Thyroid Organic Iodine, mg. I*
JD	—	33	0.056	1.4	14
FD	41	43	0.032	0.80	20
SD	—	44	0.053	1.3	31
HH	62	65	0.085	2.1	29
AL	62	46	0.022	0.56	84
HW	46	54	0.049	1.2	22
Average	53	48	0.050	1.3**	33

* Estimated on the basis of an organic iodine space for normals equal to approximately 25 l (9).

** The total I^{131} in the body (excluding the thyroid) for the 2nd day may be estimated from the fact that the inorganic iodide on day 3 is approximately 10% of the organic iodide and that on day 2 the inorganic iodide may be approximately 10 times greater than for day 3. Therefore, approximately $1.3 + (0.1 \times 10 \times 1.3)$ = approximately 2.6% dose is in the body on day 2. This value, added to the 97% recovery from the urine and uptake values, results in approximately 100% recovery of the activity for day 2.

*Recent information on normal thyroids[2] indicates that the serum organic iodine specific activity is not equal to, but is less than, the thyroid iodine specific activity 3 days after administration. The calculation of the thyroid organic iodine content, as carried out below, would lead, therefore, to an overestimate of this value.

The PBI^{131} values on the 3rd day after the administration of the dose (Table 2) range from 0.022 to 0.085% dose/1 serum and average 0.05% dose/1 serum. The value for euthyroids is approximately 0.15-0.25% dose/1 serum[1,8]. Thus, the PBI^{131} levels of these patients are lower than those of euthyroids by a factor of approximately 3 to 4. The serum inorganic iodide values were <0.005% dose/1 serum and are equivalent to approximately <10% of the PBI^{131} values for all patients; conversely >90% of the serum activity is due to the PBI^{131}. These data lead to a conversion ratio of approximately $1.0/(1.0 + 0.1) =$ approximately 0.9 which is in the normal range for euthyroids[8,9].

A question may arise about the biochemical interpretation of the PBI^{131} values. The ratio of the butanol-extractable fraction to the trichloroacetic acid-precipitable fraction is not always equal to 1, but can vary between 1 and approximately 0.6, depending on the thyroid function[6]. Since the PBI distillate used in this experiment is more nearly similar to the butanol-extractable fraction (both presumably containing iodine as thyroxine), the ratio of the distillate to the TCA-precipitable fraction will probably vary in the same manner as the ratio involving the butanol fraction. To the extent raised by the above consideration, therefore, the interpretation of the absolute PBI^{131} values is open to question. On the other hand, this consideration leads to no difficulty in the calculation of the thyroid organic iodine content, since the only requirements are that an accurate measurement be made of the specific activity of an organic iodine compartment (which in this case is the ratio PBI^{131}/PBI) and that equilibrium exists between all the organic iodine compartments. Both these requirements are not dependent on the correctness of the absolute PBI^{131} value.

Assuming that equilibrium has occurred between the specific activities of all the iodine compartments of the body, the organic iodine content of the thyroid may be calculated from the following expression:

$$\text{thyroid organic iodine} = \frac{U \times PBI}{PBI^{131}} \times 10^{-3} \text{ mg. I},$$

where U = uptake in % dose, PBI = γ I/1 serum and PBI^{131} = % dose/1 serum. The results are shown in Table 2. The values range from 14 to 84 mg. I averaging 33 mg. I. The best estimate for normals (as determined by chemical analysis of thyroid tissue) is approximately 8 mg. I[9]. Thus, the calculated thyroid organic iodine content of these patients as a group is approximately 3 to 4 times greater than that of normals. However, on the basis of Brownell's recent information[2] it would appear that the assumption of equilibrium between the specific activities is not valid and that the value of the thyroid iodine content should be between the value for normals and the maximum value calculated above (probably closer to that for normals). The conclusion may be made, therefore, that the thyroid organic iodine content of these patients is quite likely in the normal range (or on the high side of normal) but that it may be larger than for normals. The suggestion of high thyroid organic iodine stores is not inconsistent with the histological conclusion of resting colloid goiter.

Conclusion. The I^{131} uptake and excretion and the PBI values for 6 male

patients are in the normal range. Although the probably greater than normal biological half-lives and the less than normal PBI^{131} values are not significantly beyond the normal range, these results do not exclude the possibility of thyroid organic iodine stores which are greater than normal. (The high biological half-lives and low PBI^{131} values could possibly be explained by a low hormone output of the gland which, however, cannot be recognized by clinical observation.) The suggestion that there are high thyroid iodine stores is not inconsistent with the histological finding of resting colloid. As the pathological reports indicate, the weight of the thyroid was increased in most cases, in some cases more than three times the normal. Since we have evidence that the gland is uniformly enlarged in the majority of cases, the data at hand seem to indicate that the gland is operating at a lower than normal capacity but the capacity is sufficient to maintain an output which is clinically, biophysically and biochemically within normal range.

REFERENCES

1. **Brownell, G. L.:** J. Clin. Endocrinol., **11**, 1095, 1951.
2. Idem: Personal communication.
3. **Brownell, G. L.,** and **Stanbury, J. B.:** J. Clin. Endocrinol. and Metab., **13**, 210, 1953.
4. **Burns, F. J., Fish, W. A., Hackett, J. W.,** and **Hickey, F. C.:** J. Appl. Physiol., **4**, 15, 1951.
5. **Freedberg, A. S., Ureles, A.,** and **Hertz, S.:** Proc. Soc. Exper. Biol. & Med., **70**, 679, 1949.
6. **Kurland, G.:** Personal communication.
7. **Maletskos, C. J., Millen, S., Thomas, E. B., Van Dilla, M. A.,** and **Williams, J. B.:** To be published.
8. **McConahey, W. M., Keating, F. R., Jr.,** and **Power, M. H.:** J. Clin. Invest., **28**, 191, 1949.
9. **Riggs, D. S.:** Pharmacol. Rev., **4**, 284, 1952.

CONGENITAL ABSENCE OF A MAIN BRANCH OF THE PULMONARY ARTERY

By J. E. Flynn, M.D., Lt. (MC) USNR
DEPARTMENT OF INTERNAL MEDICINE

A. A. Siebens, M.D. Lt. (MC) USNR
HEAD, CARDIOPULMONARY LABORATORY

AND

S. F. Williams, M.D., Capt. (MC) USN
CHIEF OF RADIOLOGY

(From the U. S. Naval Hospital, St. Albans, New York)

Congenital absence of a main branch of the pulmonary artery has been the subject of recent reports in the literature[6,9]. Prior to the advent of present radiologic and physiologic diagnostic techniques, recognition of the anomaly depended upon postmortem examinations and on occasion, upon surgical explorations. Angiocardiography and correlated cardiopulmonary studies have demonstrated the practicability of precise definition of vascular and pulmonary abnormalities and indeed, the necessity for such studies in many patients presenting with pulmonary symptoms and unusual hilar shadows.

Case Report. The patient was a 25-year-old male officer who was referred to this hospital because of hemoptysis.

On 10 November 1953, the officer, while in the course of his usual routine, noted a tickling sensation in the throat and coughed up approximately one-half cupful of bright red blood. There were no other symptoms and it was noteworthy that the hemoptysis occurred during a period of relative inactivity. During the ensuing 48 hours the patient experienced several episodes of a similar nature. He was then admitted to a local Naval Hospital where bronchoscopy revealed the presence of fresh blood in the right main stem bronchus, but no site of the bleeding was identified. The officer continued to experience minor episodes of hemoptysis during the next few hospital days but these gradually disappeared and he was ambulated without incident. He was referred to this hospital for further study. The past medical history was significant. At the age of 9, the patient had an appendectomy which was attended by a pulmonary complication involving the right lung; a roentgenogram of the chest taken during that illness revealed an increased density in the mid-portion of the right lung field with shifting of the mediastinum to the affected side. One month later the right diaphragm was angulated upward but was otherwise considered not remarkable. (These reports were obtained from hospital records; the films were not available to the authors.) Following recovery no further symptoms occurred and the patient stated that he had considered himself quite well, having engaged in the usual sports and activities without limitations. At the age of 19, on the occasion of a routine physical examination, an abnormal chest roentgenogram (Fig. 1) was obtained. This was interpreted as revealing a shift of the mediastinal content to the right and a diminution of the volume and radiopacity of the right lung. During the next 7 years and to the onset of the present illness the patient enjoyed good health. Repeated chest roentgenograms during his Naval career demonstrated the deformity described above.

On admission to the hospital, physical examination revealed a well developed and rather muscular adult male. He appeared neither acutely nor chronically ill. The blood pressure was 136/70 and the weight was 175. Physical findings of interest included asymmetry of the thorax with evident decrease in

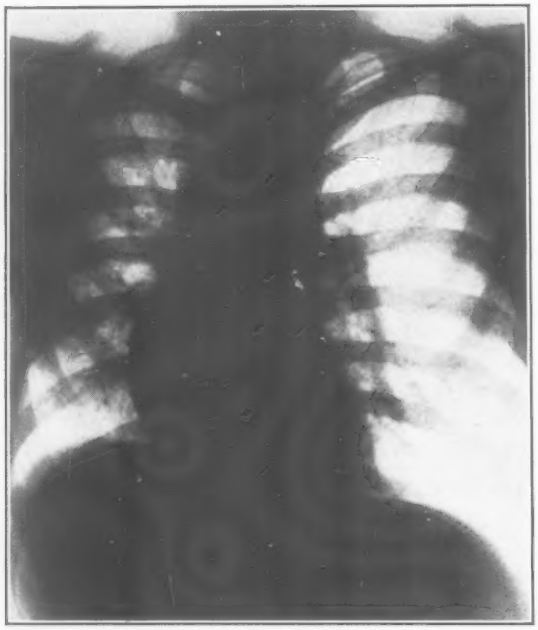


Fig. 1.—Photograph of chest roentgenogram obtained at age 19.

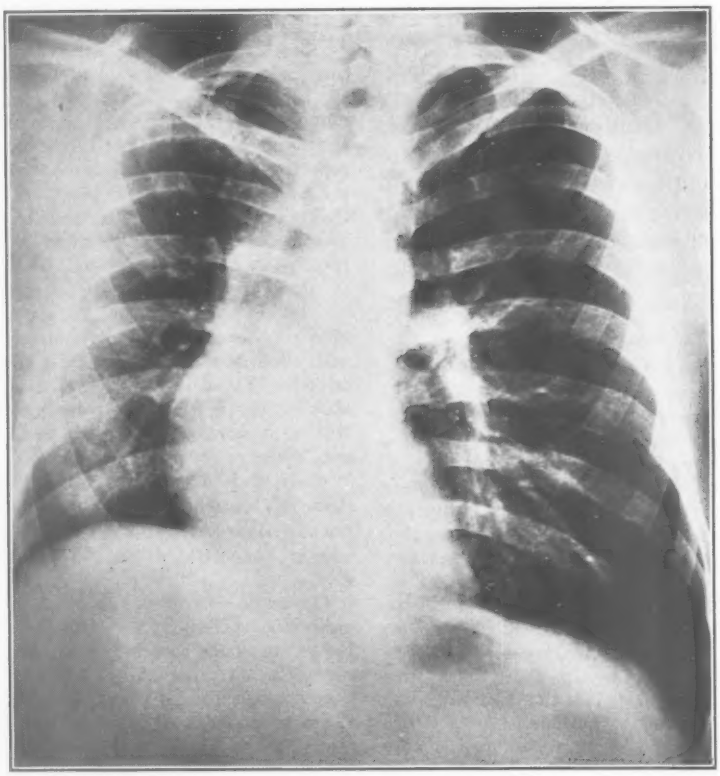


Fig. 2.—Conventional P–A projection of the chest obtained on admission to this hospital.

the size and respiratory excursion of the right hemithorax. The trachea was deviated to the right. An impaired percussion note, suggestively increased tactile fremitus, but little change in the breath sounds were noted.

The indicated routine laboratory studies were not remarkable. An electrocardiogram was normal demonstrating a semi-vertical electrical position and a prominent RS in leads V1 and V2. Routine skin tests for tuberculosis and pathogenic fungi were negative. Conventional posterior-anterior (Fig. 2) and lateral roentgenograms revealed the right chest to be considerably smaller than the left, with elevation of the right diaphragm. There were stringy markings throughout the right lung field and considerable thickening of the pleura. The heart and mediastinal structures were moderately displaced to the right and the left lung was unusually radiolucent with a small herniation of its upper lobe into the mediastinum. Tomography revealed a well delineated shadow in the position of the left pulmonary artery but did not reveal a similar shadow on the right.

At bronchoscopy, the trachea and carina were found to be deviated considerably to the right but no other abnormalities were noted. Bronchial washings were reported to be negative for malignant cells and, by culture, for acid-fast bacilli. Lipiodol bronchography demonstrated complete filling of all segments of the right lung but the bronchi so delineated were in unusually close proximity, suggesting generalized contraction of the right lung.

PULMONARY VENTILATORY STUDIES AND CARDIAC CATHETERIZATION. The only abnormal value among the tests of bilateral ventilatory function (Table 1) was the moderately reduced vital capacity, a finding in keeping with the limited excursion of the right hemidiaphragm and the relative fixation of the right rib cage observed fluoroscopically. The maximum breathing capacity was well performed in spite of this restriction. Lung volumetric relationships were within normal limits and the intrapulmonary mixing of respiratory gases was unimpaired.

Bronchospirometry (Fig. 3) revealed a marked difference in the contribution of each lung to total funcion. Although approximately 43% of ventilation at rest was performed on the right, only a negligible quantity of oxygen was taken up by this lung even when the patient was made to breathe 100% oxygen. Since oxygen uptake is related to volume flow of blood, it was concluded that virtually none of the patient's pulmonary artery stream was directed to the right lung.

In order to verify this impression, arterial puncture was performed. If the entire cardiac output were indeed flowing through the left lung, oxygenation of peripheral arterial blood should be normal, as it is following uncomplicated pneumonectomy. If, on the other hand, a significant proportion of the output

TABLE 1.—VENTILATION AND LUNG VOLUMES

Maximum Breathing Capacity	146 Liters	96% of predicted
Vital Capacity	3.53 Liters	73% of predicted
Residual Volume	1.24 Liters	103% of predicted
Total Lung Volume	4.77 Liters	79% of predicted
Residual Vol./Tot. Lung Vol. × 100	26 (normally less than 30)	
Index of Alveolar Mixing*	1.01% N_2 (normally less than 1.5%)	

		*Right Lung***	*Left Lung***
Bronchospirometry	Vit. Cap.	35	65
	Min. Vent.	43	57
	O_2 Uptake	4	96

* Concentration of nitrogen in alveolar air after the patient has breathed 100% oxygen for 7 minutes.

** Per cent of total contributed by right or left lung. Normally 55% on right, 45% on left.

were directed to the right lung, defective oxygenation of peripheral arterial blood should result, for, as demonstrated bronchospirometrically, such blood would not take up oxygen. For example, one might postulate flow to be distributed between the 2 lungs as was ventilation (43% on the right, 57% on the left). Assuming a 96% saturation of left pulmonary venous blood and a 76% saturation of mixed venous (or, in this patient, right pulmonary venous) blood, the resultant mixture should have a saturation of $(96 \times 57) + (76 \times 43)$ or 87%. Brachial artery blood was actually found to be 95.3% saturated at rest on one occasion (content 18.39 vols. %, capacity 19.29 vols. %) and 95.7% on another (content 18.38 vols. %, capacity 19.20). The evidence that blood flow through the right lung was minimal or totally absent was, therefore, convincing.

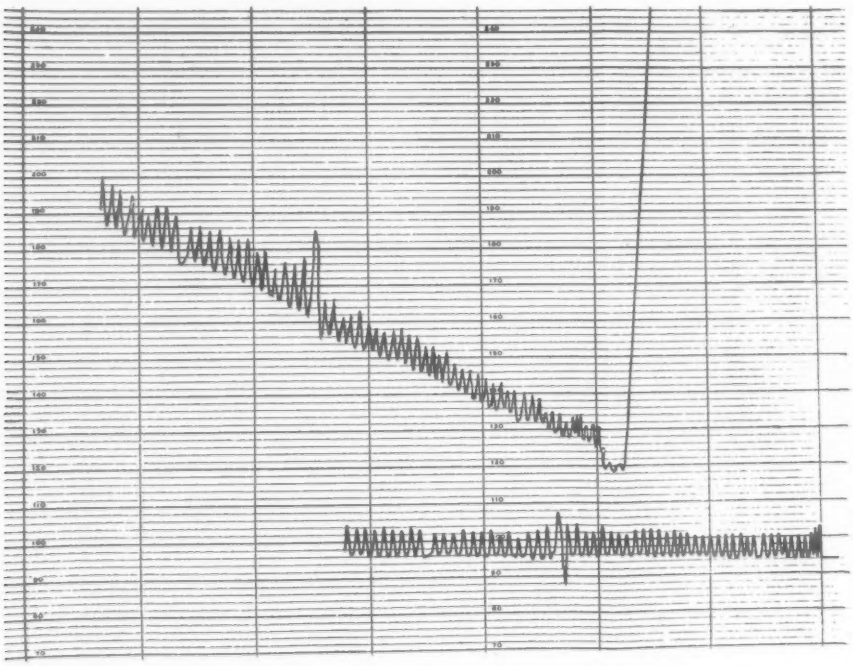


Fig. 3.—Bronchospirometric record of ventilation and oxygen consumption with the patient at rest. Upper tracing, is that of the left lung, lower tracing of the right lung. The slope of each recording is a measure of oxygen consumption. Note that although the right lung is well ventilated, it takes up almost no oxygen. Horizontal axis is time in minutes.

It was reasoned that such obstruction could be either structural or functional. Absence or stenosis of the right pulmonary artery can be cited as structural causes whereas sufficiently increased vascular resistance in the parenchyma could conceivably result in a similar block in the absence of a primary anatomic deformity. In order to test the patency of the right pulmonary artery and to measure pressures in the patient's lesser circulation, right heart catheterization was performed (Table 2). Numerous attempts at passing the catheter into the right artery were un-

successful. It was concluded, therefore, that the orifice of the right pulmonary artery was probably narrower than the catheter tip (No. 8) and that the virtual absence of flow on the right could presumably be ascribed to a structural defect.

Pulmonary artery pressures were minimally elevated (Table 2), a finding in keeping with what has been re-

Fig. 4.—Angiocardiogram. Frontal projection, demonstrating absence of the right pulmonary artery.

TABLE 2.—GAS EXCHANGE AND PULMONARY HEMODYNAMIC DATA

Arterial O_2 Content Vols. %	*Mixed Venous O_2 Content Vols. %*	*A–V Difference Vols. %*	*O_2 Consumption cc./min.*	*Pulm. Blood Flow L./min.*
18.38	14.62	3.76	302	8.03

Body Surface Area m^2	*Cardiac Index*	*Saturation*		*R. Q.*	*Pulm. Art. Pressure mm. Hg.*		
		Arterial Per Cent	*Venous Per Cent*		*Syst.*	*Diast.*	*Mean*
1.94	4.14	95.7	76.1	.76	35	14	22

corded in patients with pneumonectomies[3] or large bilateral pulmonary resections[8].

ANGIOCARDIOGRAPHY. (This procedure was performed by I. Steinberg, M.D., at the New York Hospital, New York, New York). Angiocardiography in the frontal projection (Fig. 4) demonstrated complete absence of right pulmonary artery flow. The main pulmonary artery continued as a single trunk into the left lung. Simultaneous with opacification of the aorta, at about 7 seconds, and thereafter, there appeared faint opacification of a fine network of vessels in the right lung, interpreted as a demonstration of bronchial artery circulation in the right lung.

Comment. This case was thought to be worthwhile presenting, both because the anomaly is an unusual one and because the usefulness of physiologic and roentgenographic techniques in establishing the diagnosis clinically is illustrated. Inasmuch as reviews of the literature are included in recent publications[6,9], discussion will be limited to a few points.

Absence of the right pulmonary artery was first suspected during examination of a routine chest roentgenogram taken because the patient complained of hemoptysis. Particularly suggestive were the reduced size of the right lung and hemithorax, the abnormal hilar shadow, and the increased radiolucency of the left lung with herniation through the mediastinum. Similar findings were characteristic of cases reported by others[6,9], and have been proposed as being pathognomonic of the anomaly.

The cause of hemoptysis, a common complaint among such patients, was not established. Enlargement of the bronchial arteries has been produced in dogs by ligating a main branch of the pulmonary artery[2] and has been reported in patients with diminished pulmonary artery flows, as in pulmonic stenosis[1] or congenital absence of the pulmonary artery[7]. Rupture of an atherosclerotic bronchial vessel was established as the cause of death in one patient so afflicted[4]. Although attempts at measuring bronchial artery flows have been made[6] in one patient with congenital absence of the right pulmonary artery, satisfying the steady state requirements for applying the Fick principle[5] appeared to be so difficult under the conditions described as to raise doubts concerning the high flows calculated. Nevertheless, the documented changes in the anatomy of the bronchial vasculature would seem to offer a reasonable basis for hemorrhages such as this patient experienced. Were these to become severe, pneumonectomy would be indicated.

It should be noted that this condition is compatible with considerable longevity, one patient having been reported living at the age of 56.

Summary. An instance of congenital absence of a main branch of the pulmonary artery has been described. Pertinent radiographic findings have been stressed as diagnostic criteria. The use of cardiopulmonary and angiocardiographic studies in demonstrating the physiologic and anatomic defect has been illustrated.

REFERENCES

1. **Bing, R. S., Nandam, L. D.,** and **Aray, F. D., Jr.:** Bull., Johns Hopkins Hosp., **80,** 121, 1947.
2. **Bloomer, W. E. Harrison, W., Lindskog, G. E.,** and **Liebow, A. A.:** Am. J. Physiol., **157,** 317, 1949.
3. **Cournand, A., Riley, R. L., Himmelstein, A.,** and **Austrian, R.:** J. Thoracic Surg., **19,** 80, 1950.

4. **Findlay, C. W., Jr.,** and **Maier, H. C.:** Surgery, **29,** 604, 1951.
5. **Fishman, A. P., McClement, J., Himmelstein, A.,** and **Cournand, A.:** J. Clin. Invest., **31,** 770, 1952.
6. **Madoff, I. M., Gaensler, E. A.,** and **Strieder, J. W.:** New England J. Med., **247,** 149, 1952.
7. **Manhoff, L. J., Jr.,** and **Howe, J. S.:** Arch. Path., **48,** 155, 1949.
8. **Siebens, A. A., Smith, R. E.,** and **Storey, C. F.:** Surg. Forum: Clin. Congress Am. Coll. Surg. IV. Philadelphia: W. B. Saunders, 1953.
9. **Steinberg, I., Dotter, C. T.,** and **Lukas, D. S.:** J. Am. Med. Assn., **152,** 1216, 1953.

PROGRESS
OF
MEDICAL SCIENCE

PEDIATRICS

UNDER THE CHARGE OF

IRVING J. WOLMAN, M.D.
ASSOCIATE PROFESSOR OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA

AND

ALFRED M. BONGIOVANNI, M.D.
DIRECTOR, ENDOCRINE DIVISION, CHILDREN'S HOSPITAL OF PHILADELPHIA
ASSISTANT PROFESSOR OF PEDIATRICS, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

GENETICS IN PEDIATRIC DISEASE

BY BARTON CHILDS, M.D.*
ASSISTANT PROFESSOR OF PEDIATRICS, JOHNS HOPKINS UNIVERSITY
MEDICAL SCHOOL, BALTIMORE, MARYLAND

EVEN a cursory inspection of the biological and medical literature of the day reveals a preoccupation with problems of a genetic nature. This may be due to the lessening pressure on research workers for solution to the mysteries of infections and nutritional diseases, but it is also certainly due in part to the refinement of the techniques and methods available to study biochemical and physiological processes in organisms of many types. As a result, the availability of knowledge concerning metabolism has meant that approaches to hitherto unassailable problems have suggested themselves, and the nature of the action of genes is being elucidated especially in bacteria, fungi, and to some extent in mammals including humans[51].

The purpose of this paper is to review some current concepts of genetics as they relate to humans. It is not intended as a summary of all investigations into the nature of inheritance but examples will be chosen which seem illustrative.

In the 50 years since the rediscovery of Mendel's work a considerable body of information has accumulated pertaining to the inherited variability of human beings. In general, these studies have taken the following directions: 1) The analysis of pedigrees to determine the mode of inheritance of traits or disease characteristics; 2) the epidemiological approach including statistical analysis of family data, twins, linkage studies, population genetics including gene frequencies and mutation rates, differential fertility and the effects of natural selection; 3) cytogenetics including chromosome patterns and aberrations, (though this area has been little studied); and 4) biochemical genetics in which apparently inherited

*John and Mary Markle Scholar in Medicine.

conditions have been studied from the metabolic viewpoint with an eye to determining insofar as possible the mechanism of action of mutant genes.

To consider all these areas would be well beyond the limits of a review such as this. Those aspects of greatest interest, notably the contributions in the field of inherited metabolic aberrations, will be stressed.

GENE ACTION. Many of the perennial questions await final answers. We do not know the nature of genes, how they reproduce, and what they do. The early conception of genes and gene action was a mechanistic one. Genes were particles strung along a chromosome like beads, and each one was thought to control some morphological characteristic. It was Bateson who first appreciated the possible relationships between genetic units and the chemical "ferments" which then interested biochemists[6]. Sir Archibald Garrod was a friend of Bateson, and together they applied the then newly rediscovered principles of Mendel to some diseases among humans, which were of a biochemical nature[42]. This early work of Garrod's led to further investigations into the nature and inheritance of a number of afflictions, culminating in his enunciation of two principles which are still valid[43]. The first was that the gene responsible for the characteristics that he studied operated through the failure of some specific enzymatically controlled step in an otherwise normal chemical process, causing the accumulation of the intermediate metabolite just preceding that step. The second thesis was an extension of the first, and suggested that all genetic variation between individuals had a chemical basis, and that just as individuals vary in their heritable physical characteristics so also might they vary in their biochemical constitution.

Much of this was, by necessity, supposition; but in the meantime work was being carried out which gave body and substance to the conception that genes operated by chemical means. This was the work of Onslow, Bassett, Scott-Moncrieff, Haldane and others[66,67], on the relationships of specific genes to the chemical structure of flower pigments. These substances are phenolic compounds, flavones and anthocyanins bound to glycoside residues. By means of appropriate breeding experiments it became apparent that single gene substitutions governed the color of the flower petals, and that color changes produced by such gene substitutions were determined by the state of oxidation, and methylation of the side phenolic ring, the position and type of the glycoside, and the pH of the cell sap. These chemical effects were inherited as Mendelian characters, and in addition it could be shown that there was a definite dosage effect depending upon whether one or two genes were present at a particular locus on one or both chromosomes. Thus for the first time it became clear that the function of a given gene was to control a unit biochemical process.

Following these observations there were many who were attracted by this hypothesis. Beadle and Tatum, working with a series of mutants of neurospora, each of which was unable to perform a particular step in a particular synthetic process, suggested that the function of each gene was to control an enzymatic step, possibly by being instrumental in the synthesis of the enzyme itself[6-8]. This they called the one gene-one enzyme hypothesis. Since then the relationship between genes and enzymes has been repeatedly demonstrated in a very wide variety of organisms[17,58,68,96,102]. Out of this work has come a number of new concepts of the nature of genes and their action. Among the most challenging of them is

the concept that despite the general randomness of the location of genes with respect to function, nevertheless, a section of a chromosome may carry out a sequence of related functions[46]. Mutations and their manifestations may be then, a consequence of chromosomal rearrangements; namely, chromosome breaks, deletions, translocations and the like, the alterations in function being due to the new relationships within the chromosomes caused by the rearrangement. Evidence in favor of this has been given by Pontecorvo[88] and Roper[92]. The latter has reported on three closely linked genes, that is, lying very closely together in the same chromosome, all concerned with consecutive steps in the synthesis of biotin. This is akin to the Rh system of alleles which according to one conception consists of three or possibly four[93] pairs of closely linked genes having related effects. It is interesting that the only suggested chromosomal aberration in humans so far reported is a possible chromosomal deletion involving this system[90].

Something is now known of the nature of the genic or the chromosomal substance. It seems clear from the work of Mirsky that the chromosomes are made up of desoxyribo-nucleic acid, that the DNA is constant in amount in all cells regardless of type, but varies precisely according to the chromosome number, and that it is bound to protein[75]. That this is the material which is the gene substance is very strongly suggested by the work of Griffith, Avery, McCarty and others who have been able to transform a nonencapsulated pneumococcus into a capsulated form by growing the former in media to which was added desoxyribo-nucleic acid obtained from capsulated strains. Such an induced characteristic becomes heritable and is passed on to subsequent generations[4,38,70]. More recently Hotchkiss has shown that the heritable trait of penicillin resistance in pneumococci may be transferred by the same means[59]. Thus the atomistic conception of genes may need some revision, but we may still think of the gene substance as controlling unit chemical processes, probably by mediating the design, formation, and efficiency of enzymes, and Beadle's one gene-one enzyme theory remains an excellent working hypothesis, whether we deal with molds or humans.

The question is, how does this kind of reasoning apply in humans? We know very little about the chemical abnormalities involved in morphological developmental defects, many of which seem to be genetically determined. Neither do we know much about the functioning of the numerous genes involved in the variation of normals: Stature, intelligence, pigmentation, resistance to disease and the like. These functions are doubtless the end results of the effects of very numerous genes acting in numberless different ways, and are therefore very difficult to approach. What is needed, and what in fact interests the medical investigator most, are very discrete, clear-cut deviations from the norm, such that the afflicted individual stands out so conspicuously that a reasonable approach to his departure may be devised. It seems clear, that for some time this type of genetic deviation will be all that we will be able to study, though the time may come when what we consider to be normal continuous variables will be amenable to chemical study, and we may be able to characterize the chemical constitution of the individual in genetic terms. At the moment the occurrence of several blood groups, the ability to taste phenyl thiourea, and the excretion of beta-amino-isobutyric acid in the urine, are the only known normal characteristics which are ap-

parently controlled by single gene substitutions and which are detected by chemical or immunologic means. But even though these traits may represent real polymorphisms in human populations they are still subject to quantitative variation, caused most likely by the other genes as well as by the external environment. In a recent study of some aspects of the Duffy blood group, Race, Sanger and Lehane showed that not only was the agglutination of Duffy-positive cells stronger when the individual was homozygous than heterozygous, but there was considerable variation in the strength of the antigens among both homozygotes and heterozygotes[89]. In the case of the ability to taste phenyl thiourea, Harris and Kalmus showed that though this represents a genuine dimorphism it is really a continuous variant, as there are about 5% of individuals who cannot be classified as taster or non-taster[54]. The renal excretion of beta-amino-isobutyric acid appears also to be a genetically controlled dimorphism. This substance, first discovered by Crumpler, Dent, Harris, and Westall[30], appears in the urine in large amount in approximately 10% of persons tested in the United Kingdom. Paper chromotography reveals that most people excrete very small amounts, so here again we have a distribution which may be continuous but bimodal. Recently Harris, testing a number of families, has indicated that this capacity is probably inherited recessively[52]. Thus in the case of most normal variation, we are beset by the problem of variants which fall into distributions which are continuous. Under these conditions it is difficult, if not impossible, to detect the expression of the many single genes involved.

This problem is less important in the case of the genetically determined diseases and we may now turn to an examination of some of these to see what is known about the modes of inheritance and gene action in some examples.

Since Garrod's work on alkaptonuria, cystinuria, pentosuria, and albinism, many new inborn errors of metabolism have been described. It might be of interest to consider whether Garrod's definition of inborn errors still holds.

PHENYLKETONURIA. One of the most thoroughly studied conditions from both the genetic and biochemical viewpoints is phenylketonuria. In this disease there is blockage of an enzyme step, with the accumulation of precursors. The principal defect is apparently the inability to convert phenylalanine to tyrosine. As a result, phenylalanine is found in inordinate amount in blood and urine. In addition a number of substances which are products of the metabolism of phenylalanine are excreted; phenylpyruvic, phenyllactic and phenylacetic acid this latter often conjugated with glutamine[113]. Recently Boscott and Bickel[18] have found a number of other substances in the urine. They found p-hydroxyphenyllactic and p-hydroxyphenylacetic acids as well as a number of orthohydroxyphenyl compounds. It is their suggestion that the ortho-hydroxy compounds represent an alternative pathway for the metabolism of phenylalanine through ortho-hydroxy phenylalanine, an analogue of tyrosine. The suggestion that the defect was failure of the enzymatic conversion of phenylalanine to tyrosine is due to Jervis[62]. He has recently given new evidence in favor of this view[63]. Using a method devised by Udenfriend and Cooper[105], who detected an enzyme in rat liver which would convert phenylalanine to tyrosine, Jervis was able to show that the livers of normal individuals performed such a function, while those of phenylketonurics did not. A possible criticism of the work, however,

is that the livers used were taken after death.

The cause of the mental defect is not known, though it has been repeatedly suggested that the accumulated phenylalanine or its products may be toxic to the brain. The case studied by Cowie[27] is suggestive. In this case only about 500 mg. of phenylpyruvic acid were excreted per day, approximately one-half the amount usually found in affected individuals. The mentality of this patient was higher than most, averaging 94 on several tests, though the Binet was 76. In addition the patient had dark hair and swarthy skin.

A new slant on the pigmentary defect has been given by Dancis and Balis[31] who present evidence that the presence of the accumulated phenylalanine interferes with the enzymatic oxidation of tyrosine to melanin by tyrosinase. This work was done by *in vitro* testing of the inhibitory effects of various amounts of phenylalanine on tyrosinase.

Thus we appear to have a true metabolic block allowing the accumulation of metabolites which are normally present but in the intact organism are rapidly metabolized, or are present in too small quantity to be detectable. Their presence, however, influences the function of several organ systems in a deleterious way, causing defects which on the surface seem not to be related. In genetical parlance a mutant gene responsible for several, apparently unrelated effects is termed a pleiotropic gene. This kind of explanation for pleiotropism is most laudable and much needed.

Genetically the condition has been well studied, and as in so many of the severely incapacitating genetically determined conditions, the gene expresses itself as a recessive[86]. It appears in one generation only and parents are usually normal. To date it may be termed perfectly recessive, since the heterozygote manifests no abnormality. This is true of many recessives, but in some cases the effect of the gene is detectable in the heterozygous state also. It is usually a trivial effect and not likely to bring the patient to the attention of the physician. It seems likely that all genes have some effect which would be demonstrable if one but had a method to detect it. Probably, as time passes and the effects of recessive genes become detectable in the heterozygotes, the words dominant and recessive will be little used and we will think more in terms of manifestations in homozygote and heterozygote. Certainly to be able to detect the presence and effects of a gene in more than one generation is the best means to be certain that a disease is indeed inherited in a particular family.

An important means of establishing inheritance in rare recessive conditions is the presence of a significant incidence of consanguineous matings among parents. This feature is well established in phenylketonuria. Munro[78], studying data on 47 families containing at least one phenylketonuric, found 5 first-cousin marriages or an incidence of about 11%. In general, when the frequency of a disease and therefore, of a gene is very low, we are more likely to find the homozygotes as offspring of related individuals. Thus the incidence of consanguineous matings among parents of affected offspring is inversely proportional to the frequency of the gene, but depends also upon the amount of consanguineous mating of the population. There are very few estimates of the incidence of first-cousin marriage in the United States[45], but the incidence must be very low. Therefore we might expect the consanguinity rate in rare disease here to be lower than in European countries or Japan, where first-cousin

marriages are somewhat commoner. In any case it is a question worth asking because it helps materially in establishing inheritance in conditions which appear superficially to be recessively inherited.

Thus phenylketonuria is an inborn error of metabolism, found in individuals homozygous for a gene that has to date been considered a perfectly recessive gene and showing a high consanguinity rate.

ADRENAL DISEASE. The adrenogenital syndrome is a problem commanding a good deal of interest at the present time in pediatrics[110], and there is evidence indicating that in most cases there is a metabolic block interfering with the synthesis of the adrenal corticoids[16]. As described by Wilkins, the condition may be caused by hyperplasia of the adrenal cortex, or by tumor, but the vast majority are of the former type, and it will be with these only that this review is concerned. The manifestations depend on the age of onset, some cases being congenital, some appearing after birth. In all cases there is virilism and increased protein anabolism due to excessive secretion of androgens. Some patients show evidence of other adrenal dysfunctions, however, some having a tendency to losses of sodium and elevation of serum K, which may cause death early in life. A few have hypertension, and occasionally some show hypoglycemia. In females, when the onset of the disease is early in fetal life, there is pseudohermaphrodism. Bartter and coworkers[5] suggested that the defect in this condition might be a block in the synthesis of compound F. This defect would stimulate the secretion of large amounts of adrenocorticotropic hormone which would in turn stimulate the production of other adrenal steroids, leading to excessive virilization. ACTH levels have been shown to be high[101], and blood corticoids low[16]. Bongiovanni[15] has shown that the most consistent finding in these patients is the presence of pregnantriol in the urine and that this substance may be elevated even when the 17-ketosteroids are not markedly elevated. Hechter and co-workers[56] have suggested that compound F is synthesized from cholesterol and the last step is the conversion of 17-hydroxy progesterone to 17-hydroxy corticosterone or compound F. Pregnantriol is probably a metabolite of 17-OH progesterone and is found in small quantity in normals, but in large quantity in the adrenogenital syndrome because of the block[16]. Thus in this case, a metabolite of the precursor immediately prior to the block is accumulated, rather than the precursor itself. It is interesting that the organism has the adaptability to metabolize an intermediate present normally in only very small quantity, thus rendering harmless or excretable by an alternative pathway, a substance which otherwise might be harmful or difficult to excrete. It seems clear in this instance that the disease we recognize is due, not to the failure of conversion of 17-OH progesterone to compound F, since the process does in fact take place sufficiently to maintain life in most cases, but to the over-stimulation of the adrenals by the pituitary, causing the secretion of an excess of androgen, with the attending virilism. The suggestion that the phenotype is due to a by-product of the defect rather than the defect itself seems to rest on firmer ground in this case than in phenylketonuria. It is of interest that substitution therapy using cortisone reverses the deleterious effects completely[110].

The genetics of this disease, on the other hand, has not been definitively analyzed. The disease has long been known to be familial and has not been reported in more than one generation.

Bentinck, Hinman, Lisser and Traut[12] have recently reviewed the literature on this aspect and suggest that the condition might be determined by a recessive gene. On the other hand, there are reports of the condition in first cousins[76], which in the case of a rare disease would be difficult to explain on the recessive hypothesis unless the parents were related. They are very few data available on consanguinity. Bentinck *et al.*[12] found in the literature two families in seven on whom the information was available in which the parents were first cousins. This is certainly a high proportion.

In general the criticisms of genetic information obtained from literature reports are two. 1) One can seldom be absolutely certain of uniformity in diagnosis. Diagnostic criteria change, and groups of cases are constantly being segregated from parent groups as new techniques become available to increase diagnostic acuity. Thus the diagnosis in all the cases being considered in a genetic study should be rigidly uniform. 2) In the analysis of genetic data, unwitting biases in the selection of cases is always a complicating problem. If the cases are taken from the literature, then one never knows the circumstances of their original selection, and in addition only certain cases, often the most dramatic ones, are reported. These problems have recently been reviewed in a symposium of geneticists under the auspices of the National Institutes of Health and the American Cancer Society[57].

Thus, though the disease is almost certainly inherited and probably recessively, the definitive evidence is lacking, nor is there any evidence bearing on the question of whether or not the gene has some action in the heterozygote. One approach might be to stimulate the presumably heterozygous parents with ACTH to see whether this might cause an abnormally increased excretion of pregnantriol. One might expect this increase to be less than that found among homozygotes, indicating a genetic dosage effect. If this or similar evidence were available, it would put the genetic hypothesis on firmer ground. In addition, the fact that some sibships contain "salt losers" and others do not, suggests a heterogeneity which might be genetic. Current ideas on the nature of gene mutation suggest that whenever a gene mutates, its specificity change is quantitative only, and not qualitative. To date, very few examples are known of genes in any organism exhibiting a change of function to one which is entirely alien. The mutant may do less, or it may do more, and there may be a number of alleles varying one from the other in a series of quantitative relationships. On the other hand, one must not reject the possibility that mutants with qualitatively altered specificity may exist; they might be lethal altogether, or it is possible that their new function is duplicated by some other gene, and they are inapparent. But, until there is good evidence for this type of gene behavior, it is worth considering the possibility of more than one mutant gene, each with its particular mode of action in cases of adrenal hyperplasia, or any other condition in which there are important biochemical differences between families.

THYROID DISEASE. Another condition, recently described[60,71,98,111], which probably represents one or more inborn errors is congenital cretinism with goiter. These individuals appear hypothyroid from birth, and usually develop goiters after a variable number of years. Radioactive iodine uptake studies show normal or marked uptake compatible with hyperthyroidism, yet the patients are unmistakably hypothyroid. This test thus distinguishes

these patients from the ordinary sporadic cretin who shows little or no uptake. In some of the cases thyroxin is present in gland and blood[60], while in others there is none, but protein-bound iodine is present. In one group of cases it could be shown that there was an organic iodide compound which was neither thyroxin nor diiodotyrosine. Wilkins[111] has suggested that the studies indicate that there is indeed an inborn error, but that the discrepancies might suggest that there are a number of defects at different points in the synthetic processes.

The kinds of familial aggregations reported imply some genetic heterogeneity. Most of the reports are either of a single case[97] or of two or more cases in a sibship. The cases reported by McGirr and Hutchison[71] are curiously different. There was one family with four affected sibs, one case who was a cousin of these, as well as cousin to two half-sisters (same mother). Thus there are three sibships, all cousins, one of which consisted of half-sisters. Consanguinity was not mentioned. If the supposed gene were causing its effects only in the homozygote, an hypothesis suggested by the pedigrees of the other families, it would require all four spouses of the three related parents to be carriers of the gene. This could be, if all the unions were of related persons. If not, in such a rare condition as this, the probability of such a random assortment would be fantastically low. It may be then that the gene in this instance acts when heterozygous. In general it may be said that phenotypes caused by genes segregating in different modes are probably due to different genes. The biochemical heterogeneity and genetic heterogeneity in these cases suggest that this may be so.

DISORDERS OF CARBOHYDRATE METABOLISM. If genes do in fact control the synthesis or behavior of enzyme systems, it is not much of a flight of fancy to imagine that any enzyme system might be affected by mutation of the gene or genes controlling its activity. Clearly, a major alteration or even any change in some enzymes would lead to death, or even failure of conception, and so doubtless many possible metabolic defects will never come to our attention.

As has been mentioned, microbiologists have produced strains of organisms containing mutant genes interfering with several consecutive steps in the synthesis or degradation of a particular substance. It is interesting that in the human we have defects resulting from mutants interfering with the synthesis and breakdown of glycogen. An examination of the various types of glycogen disease reveals a series of defects caused by failure of specific enzyme systems involved in the synthesis and degradation of glycogen. These phenomena have been well reviewed by G. T. Cori, C. F. Cori, Andersen, and Najjar[18,23,26,79]. The different types of glycogen disease can be correlated with abnormalities in these processes. 1) In one type, glucose-6-phosphatase activity is markedly reduced. This enzyme is responsible for the formation of glucose from glucose-6-phosphatase which is in turn a product of the breakdown of glycogen. It is therefore, necessary for the maintenance of normal levels of blood glucose. When this enzyme is absent or diminished, glycogen accumulates in liver and kidney, and hypoglycemia is a consistent feature of the disease. It is interesting to note that liver and kidney are the only structures in which this enzyme is found. In this type of the disease, the glycogen is structurally and otherwise normal. 2) In a second type of the disease there is generalized deposition of normal glycogen in many tissues, most notably the heart, striated muscles, and liver, but involving also most of the other

tissues. In this condition there is no hypoglycemia or acidosis, and death is usually due to failure of the heart. Measurement of glucose-6-phosphatase reveals a normal complement of this enzyme and the glycogen structure is normal. Thus the enzyme defect is not known, but G. Cori has suggested that a moderate decrease in the breakdown of glycogen with normal formation would lead to storage[26]. She has suggested that a defect in phosphohexoisomerase, an enzyme responsible for the reversible conversion of glucose-6-phosphate to fructose-6-phosphate, might fulfill this hypothesis. 3) and 4) In the third and fourth types, clinical manifestations are much the same, that is, there is deposition of glycogen in liver, muscle, spleen and reticuloendothelial system. This glycogen appears to be abnormal in some way in that wherever it appears it produces a fibrous response and in the liver it causes cirrhosis. Analysis of the structure of the glycogen in these cases by Illingworth and Cori[61] revealed that in one case the branch structure of the molecule was altered in the direction of very short outer branches. This suggested a defect of "debrancher" enzyme (amylo-1-6-glucosidase), which is responsible for breaking the 1-6 linkages of glucose residues in glycogen. In another case the structure of the glycogen was again abnormal, having a branch structure similar to amylopectin, that is having very long outer chains, and fewer branches. The suggestion is that in this case there is a deficiency of "brancher" enzyme, or amylo (1,4-1,6) transglucosidase. This substance is responsible for converting 1-4 linkages of glucose residues to 1-6 linkages, thus forming the branches, and together with phosphorylase which forms the 1-4 linkages, produces glycogen from glucose-1-phosphate.

Thus there are several probable enzyme defects in this group of conditions. These may not be all that exist, and study of new cases may well reveal others.

It is certainly common to find more than one case in a sibship, and it is always the same type of disease. Each condition has therefore been considered the result of a gene in the homozygous state. There are no accounts of mild forms or partial expression suggesting action of a gene in the heterozygous state. Since all of these conditions are very rare, consanguinity would be expected, and this has been mentioned in a number of cases[36,37,107]. In many reports it is not mentioned. It does seem likely that many if not all of these conditions are genetically determined, but it could easily be that some are not genetic in origin. It is well known that environmentally produced phenocopies mimic the effects of genes and it may, in the individual case, be impossible to differentiate. In the final analysis the ultimate proof of inheritance of a trait lies in appropriate breeding experiments. In humans, however, we must rely on statistical analysis of large bodies of data, on consanguinity, and expression of the gene in the presumptive heterozygote.

Another condition affecting glycogen stores is galactosemia. In this condition there is an inability to utilize galactose which accumulates in blood and urine. Hepatomegaly with cirrhosis and glycogen storage, mental defect and cataracts may result. Removal of milk from the diet causes the galactose to disappear from blood and urine, and any injuries which are reversible will disappear. The galactose tolerance test, however, which shows a high, prolonged curve, remains abnormal, and may do so for many years[103]. The cirrhosis, mental defect and cataracts may be the results of toxic effects of the accumulated galactose. The metabo-

lism of galactose has recently been clarified by Leloir and colleagues[22,104]. Galactose is converted to galactose-1-phosphate in the presence of ATP and galactokinase. The galactose-1-phosphate then reacts with uridine diphosphate glucose to produce uridine diphosphate galactose and glucose-1-phosphate, through the action of an appropriate enzyme. The uridine diphosphate galactose is then converted to uridine diphosphate glucose in the presence of the enzyme waldenase. A breakdown in any one of these three steps might prevent the utilization of galactose, causing it to accumulate, and perhaps, as has been repeatedly suggested, act as a poison. Doubtlessly other mechanisms as yet unclarified could be involved.

This condition is also familial, the distribution of cases suggesting the appearance of manifestations of the disease in homozygotes[1a,11,69,85,103]. There seems to be no information on consanguinity, and very little on effects of the presumptive gene in the heterozygote. There have been recent reports concerning amino aciduria in this disease[14,44]. Urine alpha-amino nitrogen showed two- to threefold increases after oral administration of galactose, and a variety of amino acids were found. This was taken as evidence of the toxic effects of galactose on the renal tubule. Tests of this sort done on the parents of two galactosemic patients showed no such increased excretion of alpha-amino nitrogen. Thus the gene shows no effects in the heterozygote. Galactose tolerance tests on possible heterozygotes might be interesting.

An interesting derangement of carbohydrate metabolism is shown by some cases of hypoglycemia reported by McQuarrie and coworkers[72,73]. These were all individuals on whom the diagnosis of idiopathic hypoglycemia was made only after all known mechanisms were excluded by appropriate testing. In general there were two types, those in whom there was periodic hypoglycemia accompanied by pallor, sweating, dizziness and convulsions, and those whose hypoglycemia was constant, but who also had attacks of the above type. It was of interest that in two cases of the latter type, a brother and sister, sections of pancreas showed absence of the alpha cells in the islets of Langerhans. Treatment with ACTH was successful in both types.

It has been suggested that the alpha cells of the pancreas secrete a hyperglycemic factor, which has been shown to act as a hormone activating the phosphorylase system which is involved in the conversion of glycogen to glucose 1-phosphate[100]. Presumably if the alpha cells are absent or reduced, there would be some difficulty in this reaction, due to the lack of hyperglycemic factor and hypoglycemia might result. Something along this line is suggested to explain the group of cases showing absence of alpha cells. The other cases remain unsolved. Possibly a defect in phosphorylase might account for some.

Many of these cases were familial[3], and at first glance, the genetic mechanism suggested would be a gene manifesting itself in the homozygote. In one family, however, there were three sibships (all first cousins) and, as we have seen before, this is hard to reconcile with the homozygous hypothesis. Insulin sensitivity tests on parents revealed abnormalities in one parent. This suggests that the suspected gene manifests itself in fact in the heterozygote, and for some reason the affected parent was only slightly affected. In another family in which only one sibship contained affected children, one parent was again found to have an increased sensitivity to insulin. Thus the suggestion is made that

the condition is the result of a mutant gene expressing itself variably in the heterozygous state, although equally likely is the hypothesis of a gene expressing itself partially in the heterozygote and fully in the homozygote.

This kind of variability of expression of dominant genes within families is a common phenomenon. These are the conditions which commonly "skip a generation" or two, and in which there are likely to be wide variations in expression within sibships. This is perhaps not surprising, since the effects of any gene may be modified by the genotypic environment in which it finds itself. Different genotypes would then have different modifying actions upon the effects of genes, enhancing sometimes, suppressing in others. It has been suggested that natural selection, in its effort to limit wide variability, will choose those genotypes whose modifying effects on deleterious genes are favorable[39]. This might mean that genes which had a deleterious effect in the heterozygote would become suppressed in time and come ultimately only to manifest in the homozygote. This subject has been much argued by geneticists and may not yet be solved, but it is certainly true that genes which can produce obvious effects in the heterozygote vary more widely in their expression than those whose effects are readily apparent only in the homozygote.

In the case of the hypoglycemias, it must not be lost sight of that the genes causing the two clinical types may be entirely different and that some of the sporadic cases might not really be genetically determined at all.

If genes control enzymes, the elucidation of mechanisms would be made much easier if one could measure the enzyme involved. This we may do in some of the cases of glycogen disease, but seldom in other types of disease. A recent report, however, of a new type of rickets indicates that the etiology of the condition may consist of deficiency of alkaline phosphatase in all the tissues[95]. These children have intractable rickets and premature shedding of the teeth. The serum calcium and phosphate are normal; the alkaline phosphatase is extremely low. Treatment of the rickets was unavailing. Several cases were reported from five sibships. In two families, when serum alkaline phosphatase was measured on both parents, these values were abnormally low. In one family in which both parents were tested only one parent showed a low value. In one family only the mother was tested and she showed a low value, and in one family neither were tested. These observations do indeed suggest the action of a mutant gene having the effect in the heterozygote of reducing the alkaline phosphatase in the tissues, and in the homozygote of altering bone growth and dental development as well.

What, precisely the effects of mutant genes on their enzymes might be is not known with any certainty. In general the specificity of the mutant gene will be the same as normal alleles, but it may produce alterations of a physicochemical nature in the enzyme which alters its behavior. It has been suggested that such enzymes might have reduced half-lives and become more readily denatured, or become inactivated by minor environmental changes which would not alter the normal enzyme[23]. Comparative studies of the enzymes of mutant and wild type organisms are being carried out to detect differences of physical or chemical nature. In the case of one mutant, a particular enzyme appeared to be lacking in intact cells, but appeared in extracts of the same cells[108]. In the case of the above mentioned disease it might be possible to test the alkaline phospha-

tase of the affected individuals to see how the enzyme itself compared in its properties with that obtained from normals.

All the conditions so far discussed have appeared to represent metabolic blocks in synthetic or degradation processes, or to involve directly some enzyme system, thereby fulfilling, with modifications, the criteria of gene-enzyme relationships suggested by Garrod, and Beadle and Tatum. There are many other diseases and defects in which the mechanism is not so clear, though one might suppose that they are ultimately enzyme defects. This is a common situation in genetics, and often we find that we only know of the presence of genes by effects which are many steps removed from their immediate effects, whatever they may be. Thus, in such instances we must express the mechanism as we understand it, and this may not be in terms of enzyme blocks.

FAMILIAL JAUNDICE. Crigler and Najjar[29] have reported on a new syndrome which they have called "familial nonhemolytic jaundice with kernicterus." In this condition, the affected infant becomes deeply jaundiced immediately after birth and remains so throughout his life. Seven out of eight reported cases showed neurological changes indistinguishable from kernicterus, and all of these died after a few months of life. One child only of this group remains alive and while normal in every other way, he is, at the age of 4 years, still deeply icteric. None of the usual causes of jaundice could be incriminated. There was no obstruction, no liver disease, no increased hemolysis, and all studies gave normal results, except the bilirubin tolerance test which showed abnormal retention. Serum bilirubin levels in all cases were found to vary between 15 and 40 mg. per 100 cc. though there was not much day to day variation in any one case. Urobilin excretion was normal. Extensive analysis of the properties of the bilirubin obtained from these cases and comparison with bilirubin from other types of jaundice revealed that the pigment itself was in no way different or altered[80,81]. The authors' suggestion was that the only physiological abnormality was in the inability of the liver to secrete bilirubin except in the presence of very high levels. This is then a threshold phenomenon, and the liver cannot perform this particular function until a threshold much higher than normal is reached. This is one way of looking at physiological jaundice of the newborn, and in this sense, these cases may be looked upon as developmental failures, who have preserved the infantile mechanism for the secretion of bilirubin.

Genetically the problem is most interesting. All of the parents of the three families involved were related to one another, and all stemmed from a single couple five generations previously. There has not been much movement out of or into the area in which they live, and they form, therefore, a sort of genetic isolate. There is a good deal of consanguineous mating, and given a rare gene which manifests in the homozygote, the milieu is ideal for its emergence. Thus it seems at least most likely that this is a genetically determined defect and that it manifests in the homozygote. It seems, as yet, to be perfectly recessive, since serum bilirubin levels and excretion tests on a number of parents were negative. The condition is evidently rare, and has not been previously reported, behaving in a number of particulars differently from the type of previously reported familial nonhemolytic jaundice[74].

There are other examples of mutants which are extremely rare and appear to be limited to a single family. Most

notable are the "private" red blood cell antigens named Levay, Graydon, and Dobbins, found only among members of the families of those names. Apparently the mutation is in some way an extremely rare and unusual one, with a very low rate of occurrence. The problem of mutation frequencies is a very knotty one, especially in humans. In Drosophila and other organisms in which direct methods can be used, mutation rates are seldom more frequent than 1 per 50,000 gametes, and are often much less frequent. In humans the problem is very difficult and the methods for calculation based upon many assumptions. In general it is probable that mutation rates in humans are no higher than other organisms, though in some instances it might be so[48,82,87]. This being so, the genetic material of reproducing organisms exhibits an awesome stability. If mutation rates in humans are no greater than in other organisms, one wonders how genes which are so seriously incapacitating establish themselves in relatively large numbers in the population. One answer which is by no means proven, but which must be recognized, is that, paradoxically, genes which in the homozygote are deleterious, in the heterozygous state may actually contribute favorably to the reproductive fitness of the individual carrying them. A possible example of this has been given by Allison[1], who offers evidence that persons who have sickle cell trait are more resistant to malaria than those possessing normal hemoglobin. This could explain his finding the highest incidence of the trait in those areas in which malaria was most frequent. Under these circumstances the gene causing sickle cell trait will increase in the population even in the face of selection against those individuals homozygous for that gene. If this were true, it might have some bearing on eugenic programs, and the offering of advice to carriers of such genes. The pitfalls of these problems have been well stated by Neel[83].

RENAL DISEASE. The control of homeostasis and excretion of water and electrolytes by the kidney is a vast subject which has received a good deal of attention of late. That these functions are genetically controlled appears likely, the assumption being based upon the observation of numerous familial defects of tubular reabsorption.

One of the most thoroughly studied conditions of this type is cystinuria. This is a condition in which the affected individual excretes large amounts of cystine in the urine. The disease is harmless except in those individuals in whom cystine stones are formed in the renal pelvis and collecting system. Dent and Rose studied urines from such patients using paper chromatographic methods and found abnormal amounts of lysine and arginine as well as cystine[35]. The levels of these amino acids in the blood are in no way altered, and Dent and Rose have suggested that this is a defect in the reabsorption of these amino acids. If this function is under enzymatic control, it is not known what enzymes may be involved. It has long been known that the condition appears in more than one member of a sibship, in one generation only, and that there is a high consanguinity rate. Harris and Warren have studied the condition extensively from the genetic viewpoint[55]. Measuring the amount of cystine in the urine of 232 individuals from 21 different families, they found that the distribution of cystine split the families into two groups. In one type of family the only individuals who excreted amounts of cystine in excess of the normal were stone formers and a few sibs of stone formers. All the rest of the relatives, including both parents, excreted amounts which fell with-

in the normal range. In the other type of family, certain relatives, including some sibs, both parents, uncles, aunts and cousins, excreted amounts of cystine which deviated significantly from the normal range, but were not so great as the stone formers and a very few of their sibs. The distribution of quantities of cystine in these individuals fell about midway between normals and stone formers. Thus, with reference to cystine excretion there were three types of people: normals, those excreting abnormal amounts but not enough to form stones, and stone formers. This suggested very strongly the segregation in the two types of family of two separate mutant genes having to do with the tubular reabsorption of cystine. One gene is perfectly recessive, and shows no abnormality in the heterozygote, the other shows a dosage effect altering reabsorption in the heterozygote, but to a lesser degree than in the homozygote. Factorial analysis of the data revealed good agreement between observed and expected ratios of affected to unaffected in both types of family, and the consanguinity rate was high in both instances, suggesting the validity of the genetic hypothesis. The question of whether the two proposed genes were alleles or at different loci was then raised. The data were insufficient to resolve the question, but suggested that there were two genes at different chromosomal loci, rather than two alleles which could occupy the same locus. Thus cystinuria, a condition which appears on inspection to be as homogeneous as any could be, seems to have a varied genetic basis. Work with the same families measuring lysine is going on in Dr. Harris' laboratory and it seems likely that other genes will come to light.

The question of multiple alleles versus separate loci will perhaps come up more frequently in human genetics. In general, genes at different loci will have different biochemical functions, though the ultimate phenotypes may look the same. Multiple alleles, on the other hand will express themselves in similar biochemical effects, but in different degrees. A case in point is the group of clotting defects consisting of hemophilia and hemophilia-like diseases[19,49]. Hemophilia has been shown to exist in mild forms, and the degree of mildness is always consistent within families. This can be put on a quantitative basis by testing the antihemophilic factor levels in the blood. These were found to be within a similar range within each family, thus suggesting a series of alleles, all at the same locus and segregating as expected within each family. On the other hand the hemophilioid states differ in their chemical and in some cases genetic characteristics, but under certain circumstances may resemble hemophilia clinically to a degree impossible to differentiate without laboratory tests. These conditions are due to the effects of genes existing at different loci. It is an interesting genetic fact that the hemophilioid state due to deficiency of plasma thromboplastin component (PTC) is caused by a sex-linked recessive gene, as is hemophilia in dogs and man.

Cystine may also appear in the urine of patients with the DeToni-Fanconi syndrome, though the amino acid pattern in the urine in this condition differs markedly from that just discussed. This too appears to be in part a defect of the renal tubular reabsorption mechanism. The condition may well be due to the effects of a mutant gene in homozygotes. Bickel and Harris have reported on the genetics involved[13]. They found an increased incidence of consanguineous matings among parents and estimated the gene frequency to be about 1 in 200, and the incidence of heterozygotes to be about 1 in 100.

The incidence of the disease they estimated to be 1 per 40,000. Gene frequency estimates in such rare conditions always indicate that the genes themselves are far commoner than one might expect, considering the rarity of the disease. A condition with an incidence of 1 per 1000, would have a gene frequency of 1 in 30, and one of every 15 people would be heterozygous for it. Thus it seems likely that nearly everyone is probably heterozygous for a number of genes which in the homozygote would produce disease. This, however, is part of the variability among humans, and heterozygousness for large numbers of genes is probably a good thing.

Dent and Harris[33] have reported an unusual family including some adults with the Fanconi syndrome. In this family there were three affected individuals, all three adults. One had the full blown syndrome, the other two appeared quite normal, but showed mild glycosuria, hypophosphatemia, aminoaciduria, and mild acidosis, without changes in the bones. These latter are probably genetically similar to the index case, but are either milder, or have not yet shown changes in the bones. There was no cystine storage in any of these cases. One wonders if this syndrome is not genetically and clinically different from the syndrome in children. The data are insufficient to guess whether this is a case of multiple alleles or genes at different loci.

Another renal tubular dysfunction which appears to be genetically determined is that type of diabetes insipidus which does not respond to the administration of pitressin. The disease has its onset at birth, and manifests itself in an excessive output of dilute urine and excessive need for water. When the intake falls short of the needs, dehydration and elevation of serum electrolytes ensue followed by vascular collapse and renal shutdown. The condition was first described by Waring, Kajdi and Tappan[109]. They described a family containing four affected sibs, all males, one of which was a half-brother of the other three, the mother being the shared parent. There was also an unaffected daughter by the first husband. Their studies indicated that renal function was intact except for the ability to reabsorb water, only 70 to 80% of filtered water being reabsorbed. This function was not improved by pitressin, but the patients were able to excrete electrolytes normally, providing enough water was supplied. This was often 5 or 6 times the normal intake. Growth and development are often retarded, and unless special care is taken to fulfill the extensive water needs, death early in life may result. The disease need not always be very severe, however, since in a family reported by Williams and Henry[112] there were a number of adults who had enjoyed good health, except for their defect.

It has been suggested that the condition is due to a sex-linked recessive gene which acts in some way to prevent the normal functioning of antidiuretic hormone on the distal tubule. Available evidence suggests that antidiuretic hormone is present in these cases, so it appears to be an end-organ defect, a conception of genetic defects suggested by Danforth in connection with an aberration of coloring in the feathers of Seabright-bantam cocks.

All of the reported cases have been males[64,109,112], with the exception of one female reported by Dancis, Birmingham, and Leslie[32]. This case was slightly different, however, in that even during dehydration there was no elevation of serum sodium and chloride, suggesting that their case might be functionally and genetically different. In support of the hypothesis of sex-

linkage, are the half-brothers, sharing the same mother reported by Waring, Kajdi, and Tappan. Since their report the mother has married twice more, and has borne an unaffected female by her third, and an unaffected male by her fourth husband. We have also followed two more families, one containing one affected male, and one with two affected males. The distribution of affected males in the pedigree offered by Williams and Henry also strongly suggests sex-linkage. Thus the genetic hypothesis in this case seems based upon fairly good grounds, but in general one needs rather extensive pedigree information to be sure. One needs to be wary of conditions in which affected males preponderate, but in which the causative gene lies not in an x-chromosome, but in one of the autosomal chromosomes. For instance, pattern baldness appears only in males, but the familial distribution is such that it seems reasonably clear that the gene involved is an autosomal dominant[53].

That we know of many other renal tubular defects which may be inherited, is perhaps a reflection of the availability and ease with which urine can be examined. New ones are being turned up all the time. In some instances the problem lies in determining whether the condition is due to a metabolic defect, or an alteration in tubular reabsorption. For example in the well known case of the Dalmatian Coach Hound, who unlike other dogs excretes uric acid rather than allantoin, there is no lack of uricase to convert uric acid to allantoin, but the renal threshold for uric acid is so low that it is excreted as such before conversion[41]. Rimington has suggested this as a mechanism to explain alkaptonuria[91]. That is, he suggests that there may be no enzymatic block in the oxidation of homogentisic acid, but an alteration in the renal reabsorption of homogentisic acid such that it is all excreted, and relatively little is oxidized. In support of this conception is the fact that the homogentisic acid in the blood is so low as almost to escape measurement. Still another condition in which the question is in doubt is xanthinuria. Dent and Philpot studied a 4-year-old girl who passed a xanthine stone[34]. Repeated chromatographic determinations showed large amounts of xanthine in the urine along with a small amount of uric acid. The serum uric acid was markedly reduced. The interpretation was that there is either absence or reduction of xanthine oxidase which will convert xanthine to uric acid, or alternatively that there is an altered renal threshold for xanthine such that it is rapidly excreted, before being converted to uric acid. The parents, a sib, and some other relatives were all found to show no xanthinuria. Thus, although there is no proof, nor any indication that the disease is inherited, it is the kind of problem which is very likely to be genetically determined, and the sort of instance in which it can prove profitable to look for minor manifestations in the parents or other presumptive heterozygotes.

PLASMA PROTEINS. When considering the renal tubular defects it is important to keep in mind that injury may produce changes causing syndromes identical to those which are primarily genetic. Or the injury may be secondary to a genetically controlled aberration, so that the gene action is not primarily on the tubular functioning. This may well be the case in Wilson's Disease[9,99]. It is suggested by Bearn and Kunkel[9] that the disease is in part due to the abnormally increased absorption of copper, which causes injury to the liver and kidney tubule, the latter altering the reabsorption of a number of amino acids and peptides. Thus in this case the tubular defect is only secondary

to the primary gene effect which has to do with the metabolism of copper. Others have not agreed with this viewpoint and have suggested that the amino aciduria and peptiduria are the result of a primary defect[24,106]. This latter, however, seems unlikely since cases have been reported in which a normal output of urinary amino acids was found. There is more evidence that a part of the genetic defect consists of marked reduction in ceruloplasmin, a component of the alpha-2 fraction of the serum proteins which is concerned with the binding and carrying of copper. This was first measured by Sheinberg and Gitlin[94], and has been confirmed[9]. This lack seems to explain the low serum copper levels, the high excretion of the metal, and its deposition in the tissues. The nature of the central nervous system lesion remains unclarified.

The genetics of the condition has been carefully and well studied by Bearn and Kunkel[10]. They studied the genetic histories of 16 families in which they found 26 cases. There was a first cousin consanguinity rate among parents of 37.5%, and if second cousins were included the rate was 62.5%. This is an extremely high rate, indicating the rarity of the gene and of the disease. The gene frequency calculated, using the figure for first cousin consanguinity among the affected families, and an estimated figure of consanguinity in the general population of 0.5%, was 0.00052, giving a disease incidence of approximately one per 3,700,000, and an incidence of heterozygotes of one per 1,000. Statistical analysis of the data indicated a good fit with the hypothesis that the disease is inherited as a recessive. Efforts to find heterozygotes or mildly affected individuals among the sibs by testing for aminoaciduria, and in a few sibs, abnormalities of copper metabolism were unrewarding. No mention was made, however, of tests of the parents. If one assumes the condition to be manifest in the homozygote, efforts to find heterozygotes should always be begun on the parents, since to fulfill the hypothesis they must be heterozygotes. If the tests to be made are difficult or time-consuming, parents are best, since it must be remembered that on the average only one-half the sibs will be heterozygous. Complete studies would of course include both.

There are other genetic defects involving fractions of the plasma proteins. Some of the blood clotting defects have already been mentioned. Among others may be mentioned congenital afibrinogenemia, a condition in which there is virtual absence of fibrinogen. Although more males than females are affected, there is no evidence of sex-linkage. The data in the literature are insufficient, but the condition is most likely a manifestation of a gene which causes loss of the factor in the homozygote and reduction in the heterozygote, since parents have been shown to have reduced fibrinogen levels. In a case reported by Frick and McQuarrie, both parents, some sibs and several aunts and uncles showed fibrinogen levels below normal values[40].

Finally, new light has been thrown on the condition termed by Bruton agammaglobulinemia[20,21]. In these cases, all males, there is no detectable gamma globulin, and the patients are unusually prone to infection. It has been recently reported that there is an absence of plasma cells in lymph nodes and bone marrow of patients with this condition[28,47]. When stimulated with various antigens these patients still failed to respond with either antibody or plasma cells. The condition is sometimes familial and may be inherited, though more data are needed. Whether or not it is a sex-linked

gene which is responsible is also not clear.

Conclusion. It might be worthwhile before closing to consider some present trends in genetics to see what the future holds.

One interesting development in cytogenetics is the work of Moore, Barr and others[77]. These workers have found that in female tissues, the sex chromatin is gathered in a mass, frequently adjacent to the nucleolus, or sometimes at the border of the nucleus of several types of cells. This phenomenon is sometimes seen in the male, but rarely. Thus it is possible to determine the actual genetic sex of individuals without reference to the morphology of the genitalia or gonads. In humans they have applied the method to skin biopsy material and have been able to determine the genetic sex of patients in whom, because of abnormalities of the genitalia, it is not obvious. This is clearly a useful tool in the elucidation of male and female pseudohermaphrodites and genetic intersexes. Further development of the methods of cytogenetics may be useful in throwing more light on chromosomal mutations. Possibly these are commoner than has been supposed.

Cytoplasmic inheritance has not been detected in man, but is well known and authenticated in microorganisms and plants. A recent report by Gross has suggested a mode of inheritance for leukemia in humans which is essentially cytoplasmic inheritance[50]. It is his conception that leukemia in some cases may be caused by a virus which enters the germ cell and is thereby passed from one generation to another. Whether or not the individual harboring the virus develops the disease will depend upon a variety of unknown environmental factors. Leukemia is known to be caused by a virus or like agent in mice and chickens and might be also in humans. Familial aggregations of leukemics are known in humans[2]. If the inheritance should be of this type the distribution of cases in families will not fit Mendelian ratios, and will look different in other ways. What is needed here is analysis of carefully collected data.

Geneticists are always intrigued by and interested in the possibility of finding the carriers of genes which express themselves more obviously in the homozygote. As has been repeatedly mentioned, this can be done by detecting some effect, sometimes trivial and unnoticed, in possible heterozygotes, but it can also be done by finding genes whose loci lie close to the one in question on the same chromosome. Because the chance of disruption of the relationship of the two genes by crossing over is reduced in proportion to the degree of proximity of the two gene loci, such linked genes are more likely to segregate together and appear together in new genotypes. Thus, within families, characteristics may be associated if the linked genes are occupying adjacent loci on the same chromosome. Thus the presence of an easily observed, common, marker gene may, in certain families, indicate the individuals who will be carrying the gene for which the search is made. It is important, however, to remember that linkage will explain the association or dissociation of characteristics within families only, not in the general population. This method has been tried and some results have been found. Recently a possible linkage between the Rh blood groups and the gene causing ovalocytosis has been detected[65]. The method has important drawbacks, however, and may not be really useful for a long time to come. But it is one of the areas in which geneticists work and will ultimately be of great importance.

Summary. It is hoped that the fore-

going will have indicated something of the nature of gene action in humans. It is evident that the effects of genes in humans are not materially different from those in microörganisms as determined by the microbiologists. Humans being more complicated organisms, gene effects are much more difficult to track down, and often we are left in the knowledge only that in some way a specific gene is responsible for a morphological or structural effect. Or the defect that we can detect or measure is several steps removed from the ultimate chemical manifestation. Again, sometimes a train of events is begun so that a variety of manifestations are seen obscuring the underlying, original fault. But in every case when one approaches the action of genes, they appear to mediate some biochemical event. Thus mutant genes provide us experiments of nature, often not imitated by acquired disease, the study of which can throw light on the normal physiological processes, since mutants generally fail to perform the function of their normal alleles. It is clear that this kind of knowledge is in its infancy, that we understand the mode of action of only a handful of mutants, and a very few normal genes. Possibly, in some future we cannot foresee, we may understand more about the genetic background of the normal constitution, and be able to express it in chemical terms. For the moment, however, it is worthwhile to attempt to determine accurately the mode of inheritance of particular genes, their action and frequency, to characterize their variability of expression, and to attempt to find in the case of recessives the genic manifestation in the heterozygotes. This latter can sometimes give a clearer idea of what the gene is doing than when it is present in double dose[84]. All this can help to direct therapy and above all prevention. Inherited diseases should be ultimately as treatable as ony other kind and prevention of disease is the aim here as in all disease. This is a better aim than eugenic programs which would prevent the conception of genotypes which contain thousands of genes all for the sake of one deleterious one. Furthermore, no one knows what the genetic needs of the distant future may be, and genes, which are thought to be harmful now, may one day help to adapt the individual to a possibly materially different environment. In the meantime we need to learn a great deal more about the nature of genic and chromosomal behavior.

REFERENCES

(1) **Allison, A. C.**: Ann. Human Genetics, **19**, 39, 1954. (1a) **Andersen, D. H.**: In Carbohydrate Metabolism, edited by V. A. Najjar. Baltimore: Johns Hopkins Univ. Press, 1952, pp. 28-43. (2) **Andersen, R. C.**: Am. J. Dis. Child., **81**, 313, 1951. (3) **Andersen, R. C., Wright, W. S., Bauer, E. G.,** and **McQuarrie, I.**: Am. J. Human Genetics, **2**, 264, 1950. (4) **Austrian, R.**: Bact. Rev., **16**, 31, 1952.

(5) **Bartter, F. C., Albright, F., Forbes, A. P., Leaf, A., Dempsey, E.,** and **Carroll, E.**: J. Clin. Invest., **30**, 237, 1951. (6) **Beadle, G. W.**: In Genetics in the Twentieth Century, edited by L. C. Dunn. New York: The Macmillan Co., 1951, p. 221. (7) Idem: Chem. Rev., **37**, 15, 1945. (8) **Beadle, G. W.,** and **Tatum, E. L.**: Proc. Nat. Acad. Sci., **27**, 499, 1941. (9) **Bearn, A. G.,** and **Kunkel, H. G.**: J. Clin. Invest., **33**, 400, 1954. (10) Iidem: Am. J. Med., **15**, 442, 1953. (11) **Bell, L. S., Blair, W. C., Lindsay, S.,** and **Watson, S. J.**: J. Pediat., **36**, 477, 1950. (12) **Bentinck, R. C. Hinman, F., Sr., Lisser, H.,** and **Traut, H. F.**: Postgrad. Med., **11**, 301, 1952. (13) **Bickel, H.,** and **Harris, H.**: Acta pediat., **42**, Supp. 90, 22, 1952. (14) **Bickel, H.,** and **Hichmans, E. M.**: Arch. Dis. Child., **27**, 348, 1952. (15) **Bongiovanni, A. M.**: Bull. Johns Hopkins Hosp., **92**, 244, 1953. (16) **Bongiovanni, A. M., Eberlein,**

W. R., and **Cara, J.**: J. Clin. Endocrinol. and Metab., **15**, 409, 1954. (**17**) **Bonner, D. M.**: Cold Spring Harbor Symposia on Quantitative Biology, **16**, 143, 1951. (**18**) **Boscott, R. J.**, and **Bickel, H.**: Scand. J. Clin. & Lab. Invest., **5**, 380, 1954. (**19**) **Brinkhous, K. M., Langdell, R. D., Penick, G. D., Graham, J. B.**, and **Wagner, R. H.**: J. Am. Med. Assn., **154**, 481, 1954. (**20**) **Bruton, O. C.**: Pediatrics, **9**, 722, 1952. (**21**) **Bruton, O. C., Apt, L., Gitlin, D.**, and **Janeway, C. A.**: Am. J. Dis. Child., **84**, 632, 1952.

(22) **Caputto, R., Leloir, L. F., Trucco, R. E., Cardini, C. E.**, and **Paladini, A. C.**: J. Biol. Chem., **179**, 497, 1949. (**23**) **Catcheside, D. G.**: Biochem. Soc. Symposia, No. 4. London: Cambridge Univ. Press, 1950, p. 32. (**24**) **Cooper, A. M., Eckhardt, R. C., Faloon, W. W.**, and **Davidson, C. S.**: J. Clin. Invest., **29**, 265, 1950. (**25**) **Cori, C. F.**: In Carbohydrate Metabolism, edited by V. A. Najjar. Baltimore: Johns Hopkins Univ. Press, 1952, p. 3. (**26**) **Cori, G. T.**: Harvey Lectures, Series 48, 145, 1952-1953. (**27**) **Cowie, V. A.**: Lancet, **1**, 272, 1951. (**28**) **Craig, J. M., Gitlin, D.**, and **Jewett, T. C.**: Tr. Soc. Ped. Res., p. 4, 1954. (**29**) **Crigler, J. F.**, and **Najjar, V. A.**: Pediatrics, **10**, 169, 1952. (**30**) **Crumpler, H. R., Dent, C. E., Harris, H.**, and **Westall, R. G.**: Nature, **167**, 307, 1951.

(31) **Dancis, J.**, and **Balis, M. E.**: Abstr. Soc. Ped. Res., p. 7, 1954. (**32**) **Dancis, J., Birmingham, J. R.**, and **Leslie, S. H.**: Am. J. Dis. Child., **75**, 316, 1948. (**33**) **Dent, C. E.**, and **Harris, H.**: Ann. Eugenics, **16**, 60, 1951. (**34**) **Dent, C. E.**, and **Philpot, G. R.**: Lancet, **1**, 182, 1954. (**35**) **Dent, C. E.**, and **Rose, G. A.**: Quart. J. Med., N.S. **20**, 205, 1951. (**36**) **di Sant'Agnese, P. A., Andersen, D. H., Mason, H. H.**, and **Bauman, W. A.**: Pediatrics, **6**, 402, 1950.

(37) **Ellis, R. W. D.**, and **Payne, W. W.**: Quart. J. Med., **5**, 31, 1936. (**38**) **Ephrussi-Taylor, H.**: Cold Spring Harbor Symposia on Quantitative Biology, **16**, 445, 1951.

(39) **Fisher, R. A.**: The Genetical Theory of Natural Selection. Oxford: Clarendon Press, 1930. (**40**) **Frick, P. G.**, and **McQuarrie, I.**: Pediatrics, **13**, 44, 1954. (**41**) **Friedman, M.**, and **Byers, S. O.**: J. Biol. Chem., **175**, 727, 1948.

(42) **Garrod, A. E.**: Lancet, **2**, 1, 73, 142, 214, 1908. (**43**) Idem: Inborn Errors of Metabolism, 2nd ed. London: Frowde and Hodder, 1923. (**44**) **Gellis, S.**, and **Hsia, O. Y. Y.**: Abstr. Am. Ped. Soc., May, 1954. (**45**) **Glass, H. B.**: Cold Spring Harbor Symposia on Quantitative Biology, **15**, 22, 1950. (**46**) **Goldschmidt, R. B.**: Ibid., **16**, 1, 1951. (**47**) **Good, R. A.**: Tr. Soc. Pediat. Res., p. 3, 1954. (**48**) **Goodman, H. O.**, and **Reed, S. C.**: Am. J. Human Genetics, **4**, 59, 1952. (**49**) **Graham, J. B., McLendon, W. W.**, and **Brinkhous, K. M.**: Am. J. Med. Sci., **225**, 46, 1953. (**50**) **Gross, L.**: Blood, **9**, 557, 1954.

(51) **Harris, H.**: An Introduction to Human Biochemical Genetics. London: Cambridge Univ. Press, 1953. (**52**) Idem: Ann. Eugenics, **18**, 43, 1953. (**53**) Idem: Ibid., **13**, 172, 1946. (**54**) **Harris, H.**, and **Kalmus, H.**: Ibid., **15**, 24, 1949. (**55**) **Harris, H.**, and **Warren, F. L.**: Ibid., **18**, 125, 1953. (**56**) **Hechter, O., Zaffaroni, A., Jacobsen, R. P., Levy, H., Jeanloz, R., Schenker, V.**, and **Pincus, G.**: Recent Progress in Hormone Research. New York: Academic Press, Inc., **6**, 215-250, 1951. (**57**) **Heson, W. E.**: Am. J. Human Genetics, **6**, 45, 1954. (**58**) **Horowitz, N. H.**, and **Leupold, V.**: Cold Spring Harbor Symposia on Quantitative Biology, **16**, 65, 1951. (**59**) **Hotchkiss, R. D.**: Ibid., **16**, 457, 1951. (**60**) **Hubble, D.**: Lancet, **1**, 1112, 1953.

(61) **Illingworth, B.**, and **Cori, G. T.**: J. Biol. Chem., **199**, 653, 1952.

(62) **Jervis, G. A.**: J. Biol. Chem., **169**, 651, 1947. (**63**) Idem: Proc. Soc. Exper. Biol. & Med., **82**, 514, 1953.

(64) **Kao, M. Y.**, and **Steiner, M. M.**: Pediatrics, **12**, 400, 1953.

(65) **Lawler, S.**: Ann. Eugenics, **17**, 262, 1953. (**66**) **Lawrence, W. J. C.**: Biochem. Soc. Symposia, London: Cambridge Univ. Press, **4**, 3, 1950. (**67**) **Lawrence, W. J. C.**, and **Price, J. R.**: Biol. Rev., **15**, 35, 1940. (**68**) **Lederberg, J., Lederberg, E. M., Zinder, N. D.**, and **Lively, E. R.**: Cold Spring Harbor Symposia on Quantitative Biology, **16**, 413, 1951. (**69**) **Lockhart, J. D.**, and **Roboz, E.**: Pediatrics, **13**, 211, 1954.

(70) **McCarty, M.**: Bact. Rev., **10**, 63, 1946. (**71**) **McGirr, E. M.**, and **Hutchison, J. H.**: Lancet, **1**, 1117, 1953. (**72**) **McQuarrie, I.**: In Carbohydrate Metabolism, edited by V. A. Najjar. Baltimore: Johns Hopkins Univ. Press, 1952, p. 76. (**73**) Idem: Am. J. Dis. Child., **87**, 399, 1954. (**74**) **Meulengracht, E.**: Quart. J. Med., **16**, 83, 1947. (**75**) **Mirsky, A. E.**: Harvey Lectures, Series 46, 98, 1950-1951. (**76**) **Money, J.**: Doctoral Dissertation, Harvard Univ. Library, p. 43, 1952. (**77**) **Moore, K. L.,**

Graham, M. A., Barr, M. A., and **Barr, M. L.**: Surg., Gynec. & Obst., **96**, 641, 1953. (**78**) **Munro, T. A.**: Ann. Eugenics, **14**, 60, 1947.

(**79**) **Najjar, V. A.**: J. Pediat., **6**, 804, 1952. (**80**) Idem: Pediatrics, **10**, 1, 1952. (**81**) **Najjar, V. A.,** and **Childs, B.**: J. Biol. Chem., **204**, 359, 1953. (**82**) **Neel, J. V.**: Am. J. Human Genetics, **5**, 154 1953. (**83**) Idem: Ibid., **4**, 332, 1952. (**84**) Idem: Ibid., **1**, 1, 1949.

(**85**) **O'Donnell, G. N.,** and **Vann, S. H.**: Pediatrics, **7**, 503, 1951.

(**86**) **Penrose, L. S.**: Lancet, **2**, 192, 1935. (**87**) Idem: The Biology of Mental Defect. London: Sidgewich and Jackson, 1949. (**88**) **Pontecorvo, G.**: Biochem. Soc. Symposia, **4**, 40, 1950.

(**89**) **Race, R. R., Sanger, R.,** and **Lehane, D.**: Ann. Eugenics, **17**, 255, 1953. (**90**) **Race, R. R., Sanger, R.,** and **Selwyn, J. G.**: Nature, **166**, 520, 1951. (**91**) **Rimington, C.**: Biochem. Soc. Symposia, **4**, 16, 1950. (**92**) **Roper, J. A.**: Nature, **166**, 156, 1950. (**93**) **Rosenfield, R. E., Vogel, P., Sanger, R.,** and **Race, R. R.**: Brit. Med. J., **1**, 975, 1953.

(**94**) **Sheinberg, I. H.,** and **Gitlin, D.**: Science, **116**, 484, 1952. (**95**) **Sobel, E. H., Clark, L. C., Jr., Fox, R. P.,** and **Robinson, M.**: Pediatrics, **11**, 309, 1953. (**96**) **Sonneborn, T. M.**: Cold Spring Harbor Symposia on Quantitative Biology, **16**, 483, 1951. (**97**) **Stanbury, J. B.**: J. Clin. Endocrinol., **11**, 740, 1951. (**98**) **Stanbury, J. B.,** and **Hedge, A. N.**: J. Clin. Endocrinol., **10**, 1471, 1950. (**99**) **Stein, W. H., Bearn, A. G.,** and **Moore, S.**: J. Clin. Invest., **33**, 410, 1954. (**100**) **Sutherland, E. W.**: In Carbohydrate Metabolism, edited by V. A. Najjar. Baltimore: Johns Hopkins Univ. Press, 1952, p. 14. (**101**) **Sydnor, K. L., Kelley, V. C., Raile, R. B., Ely, R. S.,** and **Sayers, G.**: Proc. Soc. Exper. Biol. & Med., **82**, 695, 1953.

(**102**) **Tatum, E. L.**: Fed. Proc., **8**, 511, 1949. (**103**) **Townsend, E. H., Jr., Mason, H. H.,** and **Strong, P. S.**: Pediatrics, **7**, 760, 1951. (**104**) **Trucco, R., Caputto, R., Leloir, L. F.,** and **Mittleman, N.**: Arch. Biochem., **18**, 137, 1948.

(**105**) **Udenfriend, S.,** and **Cooper, J. R.**: J. Biol. Chem., **194**, 503, 1952. (**106**) **Uzman, L.,** and **Denny-Brown, D.**: Am. J. Med. Sci., **215**, 599, 1948.

(**107**) **Von Crevald, S.**: Medicine, **18**, 1, 1939.

(**108**) **Wagner, R. P.,** and **Guirard, B. M.**: Proc. Nat. Acad. Sci., **34**, 398, 1948. (**109**) **Waring, A. J., Kajdi, L.,** and **Tappan, V.**: Am. J. Dis. Child., **69**, 323, 1945. (**110**) **Wilkins, L.**: J. Pediatrics, **41**, 800, 1952. (**111**) **Wilkins, L., Clayton, G. W.,** and **Berthrong, M.**: Pediatrics,, **13**, 235, 1954. (**112**) **Williams, R. H.,** and **Henry, C.**: Ann. Int. Med., **27**, 84, 1947. (**113**) **Woolf, L. I.,** and **Vulliamy, D. G.**: Arch. Dis. Child., **26**, 487, 1951.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

CARL BACHMAN, M.D.
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA

AND

FRANKLIN L. PAYNE, M.D.
PROFESSOR OF OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

CARCINOMA OF THE ENDOMETRIUM

BY ALFRED I. SHERMAN, M.D.
ASSISTANT PROFESSOR IN OBSTETRICS AND GYNECOLOGY; INSTRUCTOR IN RADIOLOGY

AND

A. N. ARNESON, M.D.
PROFESSOR IN CLINICAL OBSTETRICS AND GYNECOLOGY, AND ASSOCIATE PROFESSOR IN CLINICAL RADIOLOGY

(From the Department of Obstetrics and Gynecology, The Barnard Free Skin and Cancer Hospital, and The Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri)

THE treatment of carcinoma of the uterine corpus has for many years been a subject of moderate controversy. In addition to the fluid state in which the question of treatment is to be found, there has also been broad discussion upon etiology. The marked changes shown by endometrium in response to endocrine stimulation, and the similarity of certain hyperplasias to cancer, have provided speculative interest in factors responsible for the development of malignancy. The complexity of the endocrine system has prevented definition of the part that activity may play, and the relative paucity of material has prohibited the accumulation in a single clinic of sufficient data to permit accurate conclusions as to the proper therapeutic approach to this problem.

The incidence of endometrial cancer is estimated to be one-sixth to one-third that of cervical cancer. During more recent years, however, there is evidence of relative increase in the occurrence of endometrial lesions. The significance of that increase is controversial. Some authors believe that the greater use of hormones of all types is a factor of importance. Others have suggested that the application of radiation for gynecological conditions believed to be benign has some responsibility. There is general agreement that accuracy in diagnosis is improved, and, therefore, fewer cases are overlooked. One quite definite explanation is to be found in the natural history of the disease in that it tends to occur in older women. The trend toward a disproportion-

tional increase in older age groups provides a greater reservoir of prospects for endometrial cancer. More than three-fourths of all patients are over 50 years of age. That age distribution is in contrast with cervical cancer, which, to a large extent, is a premenopausal lesion. One other point should be mentioned in relation to carcinoma of the cervix. Data upon the incidence of that lesion among celibate women indicates the value to be extremely low. Any fall in incidence of endometrial cancer in that group is not marked.

The frequent association of endometrial cancer with various metabolic disturbances has been the basis for considerable research. The endocrinological manifestations of many of those associated dysfunctions has advanced the belief that the endocrines are of etiological significance. The high incidence of association with hypertension is an example of one of the conditions in question. That relationship is cited in most clinical reports, but, unfortunately, many publications fail to specify criteria for recognition of hypertension, or to give comparable data upon incidence in a control group from their general clinic population. There can be no doubt, however, but that such a relationship does exist. The same point can be made for the association of diabetes mellitus and obesity in relation to corpus cancer. In addition to those conditions, hirsutism is also recognized to have a frequent association with the disease in question.

All of the above mentioned disturbances have been linked in some way with pituitary dysfunctions. A number of authors both here and abroad have attempted to show a common endocrinological pathway for the control of those conditions by the anterior lobe of the pituitary. Such a theory is intriguing, but many discrepancies obscure continuity of the pathways. At the same time it is not surprising to find speculation upon the basic relationship of excessive anterior pituitary activity to the etiology of endometrial cancer. As a result a great deal of study has been focused upon effects of the estrogens. Most of the evidence presented in support of possible carcinogenic effects of estrogen is related to abnormal stimulation, which in many instances can be attributed to the pituitary. A review of the data at hand finds the question unanswered. In that connection mention should be made of the occasional situation in which one finds endometrial cancer associated with an elevated estrogen level resulting from the clinical administration of hormones, or from an estrogen producing tumor. Larson[7] has presented an excellent discussion of that subject with the conclusion that such as association presents the strongest argument for the carcinogenic action of estrogen in the human, but that there is no positive evidence to prove that effect, nor to prove any similar action from other related factors such as the pituitary.

The rather frequent history of a late menopause among patients with corpus cancer, and the relatively high incidence of nulliparity and sterility, also suggest the endocrine system as a causative agent. Despite absence of evidence showing a direct relationship one cannot dismiss the possibility of an hereditary potential for abnormal growth that may act as the trigger mechanism. The suggestive and suspicious associations produce a provocative frustration that is augmented by the wide range in responses found normally in endometrium, and the histologic similarity of benign hyperplasias to recognizable cancer.

It is not uncommon for a patient with endometrial cancer to present the history of previous irradiation for a supposed benign condition. Realizing

the traumatic and carcinogenic effects of radiation one might easily assume the earlier treatment to be a factor of importance in the development of the disease. Evidence is lacking to prove direct transition to cancer due to the use of either Roentgen rays or radium. In spite of this apparent relationship it is more logical to attribute the association to coincidence, or to transitional stages toward cancer not recognized at the time of irradiation. The practical point to be emphasized here is the need for precision in diagnosis, and the hazard incurred by oversight in the selection of radiation for the control of bleeding, or tumors believed to be of benign origin.

Clinical symptoms of corpus cancer are not peculiar to that disease. Abnormal bleeding is by far the most frequent and important symptom. In the premenopausal patient there may be menorrhagia with or without intermenstrual bleeding. Postmenopausal bleeding requires the most careful investigation. A symptom of particular significance is the presence of thin watery discharge, frequently turbid and often malodorous, and sometimes believed by the patient to be an abnormal escape of urine. Pain, loss of weight, weakness, and the like are late symptoms usually associated with tumor spread and invasion, except in some instances of severe infection.

Definitive diagnosis depends upon microscopic examination of tissue removed for biopsy. Any diagnosis made upon clinical evaluation alone is always inconclusive. Frozen sections are impractical in the recognition of endometrial lesions. Vaginal smears are helpful for screening purposes, but the method is not reliable for definitive diagnosis. Endometrial biopsy performed in the office or in the clinic may establish diagnosis if a specimen of tumor is procured, but a negative section should never be accepted as a final diagnosis. Curettement of the uterine cavity is the only means by which tissue representative of the whole endometrium can be obtained, and even with that procedure it is possible for a small lesion to escape detection. Mention should be made of the practice followed by some in performing curettement and applying radium at the same operation if tissue removed from the uterus appears grossly to be malignant. Such a procedure needs to be condemned. There is not only risk of error in recognition of cancer, but as will be seen later histologic characteristics of tumor are of importance in planning treatment. Furthermore, the data obtained at currettement upon size and configuration of the uterine cavity are of great importance in selection of intrauterine radium applicators. The information gained by curettement far outweighs the questionable deterents of possible dispersion of the tumor, extra expense to the patient, or brief delay in the application of definitive therapy.

As a general rule the rate of growth of corpus cancer is relatively slow, at least in comparison with some cervical cancers. Extension beyond the uterus by direct invasion, or spread by lymphatic or vascular dispersion is believed to be relatively late. Recently, however, Henrikson[3] and also Javert[6] have demonstrated the tendency to spread to be greater than is generally believed. Tubal and ovarian metastases are not infrequent, and increase the probability for lymphatic dispersion to lumbar and aortic nodes. Vaginal metastases are not uncommon, and appear often in the region about the terminal portion of the urethra. Many corpus cancers invade the cervix. Mention should be made here of the importance of fractional curettage in performing that diagnostic procedure. Invasion of the

cervix depreciates prognosis considerably. It is important that scrapings from the cervical canal be kept separately for examination. So frequently does corpus cancer invade the cervix that about half of the clinically evident glandular cancers of that structure will be found to be due to downgrowth of endometrial cancer. Microscopic distinction between primary adenocarcinoma of the cervix and endometrial cancer is always difficult. Finally, mention should be made of the ability of endometrial cancer to implant readily. Curettement should be performed carefully, and retraction of the vagina accomplished without trauma to the epithelium. A small tear or abrasion of that structure may be contaminated with tumor and become the location of an apparent metastasis.

The belief that endometrial cancer tends to remain within the limits of the myometrium has prompted the recommendation that hysterectomy alone is adequate treatment. Many patients not suited to surgery must be irradiated, and the clinical results obtained by some have led to the conclusion that Roentgen rays and radium can be used effectively in operable patients. Other authors, chiefly in this country and to a lesser extent abroad, have advocated the combined use of radiation and surgery with extension of the group to whom hysterectomy is applied. Comparative evaluation of the three types of treatment is hampered by paucity of clinical material, and made complex, by difficulties in classification of stage of advance, and by effects of natural history upon prognosis. It is not surprising that disagreements have arisen, and that selection of method of treatment remains a rather fluid problem.

Accessibility to palpation of the normal pathways of tumor spread for cervical cancer has made possible rather precise estimation of stage of tumor advance for clinical classification. Patients can be divided into groups of fairly uniform material for reporting results. The classification of corpus cancer is more difficult, and no standard plan has been widely adopted. Several methods for clinical grouping have been suggested, but none fulfill all requirements for adequate clinical standardization prior to therapy. One of the criteria suggested, for example, is size of the uterus, but whether determined bimanually or by sounding the uterus, that measurement is not apt to provide an accurate estimate of tumor extent. Other factors, such as myomas, may affect uterine size. Likewise, extensions outside the uterus are not always recognizable upon the basis of uterine fixation, or adnexal enlargement. There are many benign causes for those changes. Histologic groupings have been suggested, and those data are of value in estimating prognosis, but microscopic appearance of a biopsy specimen does not indicate the degree of tumor spread. Classifications made upon the basis of findings after hysterectomy are of considerable accuracy, but those are not applicable to patients not treated by surgery. The World Health Organization under the direction of Professor Heyman is undertaking a study of the problem, and may report a satisfactory solution.

The most practical classification so far proposed is one that has been suggested by Heyman[4,5]. Selection of operability is made dependent upon individual judgment of extent of tumor, individual appraisal of the general physical condition of the patient, and surgical facilities available at the particular institution in question. Patients presenting lesions believed to fall within an operable stage are divided into two groups. The first, termed "Clinically Operable," includes those in physical condition sufficiently good to justify

performance of surgery. If other associated constitutional disorders contraindicate hysterectomy the patient is considered "Technically Operable." If extent of tumor makes operative treatment impractical the patient is classified as "Inoperable." Corpus cancers with cervical involvement, or those with large ovarian tumor masses, or any others in which the site of the primary growth may be indefinite, are kept separately for all statistical purposes.

The lack of standardization in clinical classification complicates the comparison of results given in different reports. Evaluation of results is made more complex by variation in techniques of treatment. That will apply to irradiation as well as surgery. Specification of radiation dose is difficult, and even if given in terms of roentgens, or in percentage depth doses, the data are not transposable without knowledge of other physical factors such as quality, intensity, period of irradiation, and others. Furthermore, treatment may include the use of external irradiation (Roentgen rays, or radium, or cobalt applicators), or that form of irradiation may be entirely omitted. Radium treatment may vary from a simple intrauterine tandem, or special applicators holding several sources, to the special packing technique devised by Heyman for the use of multiple capsules introduced singly into the uterine cavity to fill all available space. There is considerable variation in the distribution of radiation for the several radium techniques that may be employed. Similarly, techniques and extensiveness of surgery may range from simple hysterectomy to radical hysterectomy with removal of lymph nodes, and with variable precautions that are taken to prevent tumor spread. It is obvious that considerable difference will be found in extent of vaginal segment removed at operation, which is one of the more frequent sites of recurrence. All of those differences in treatment, as well as difficulties in clinical staging, complicate evaluation of results. It can be seen that controversy in choice of method of treatment is apt to arise, and there is no surprise in the statement made by Novak[8] that treatment of corpus cancer remains a fluid problem. It should be noted, however, that the controversy applies only to operable patients.

Upon the basis of survival rates the proponents of surgery alone present excellent results to support their belief. The pertinent question is whether the use of radiation in conjunction with surgery will improve results over those obtained by hysterectomy alone. A number of authors are of the opinion that neither Roentgen rays nor radium have improved their results in clinically operable patients. In some instances that conclusion seems to have been made after the use of amounts of radiation that appear to be inadequate. The experience of other authors indicates that the combined treatment will improve results, in fact a few individuals have suggested that irradiation can be sufficiently adequate to supplant operation. That assertion does not appear warranted in view of the radiation failures noted in patients operated upon after the application of Roentgen rays and radium. Heyman[4,5] has reported a number of such cases in his radiologically treated series. He has, however, demonstrated conclusively that many patients may be cured by irradiation alone.

Another point of debate upon the combined treatment has been the relative importance of radiation and surgery. It is somewhat illogical to employ radiation if hysterectomy is the more definitive procedure. If the combined treatment actually does improve clinical results, then explanation of the

mechanism for that improvement becomes vague. Criticism has been given upon the basis that preoperative irradiation delays performance of the more definitive treatment, and that in the interest of lower morbidity one is obliged to employ lesser amounts of radiation than are required for tumor control. There is also apt to be a greater amount of fibrosis in the pelvis following both methods of treatment. Those statements are generally true, but there is rarely any added technical difficulty in performance of surgery, nor any special problems in wound healing. The vaginal vault may show considerable reaction for a longer period after hysterectomy, and if vaginal hysterectomy is employed there may be loss of superficial epithelium by necrosis.

In the attempt to arrive at some advance in answer to the many questions involved, we have reviewed the patients with corpus cancer treated during the period 1930-1948 at the Barnes and at the Barnard Free Skin and Cancer Hospitals. A total of 260 primary cases are available for 5-year survival study. During the years involved there has been a period of definitive treatment for operable cases by hysterectomy alone, as well as one through which the combined treatment has been employed. Throughout the time in question there are a few clinically operable patients treated only by surgery. Clinical classification of the patients at each institution has been made by a group of physicians comprising essentialy overlapping staffs. The patients are chiefly clinic cases, but private patients treated at the Barnes Hospital are included. From the entire series a few patients failing to return for complete treatment have been excluded from the review.

Of the entire group of 260 patients, 112 were treated by irradiation alone. Fifty-seven were treated by surgery alone, and 91 received the combined treatment of preoperative Roentgen rays and radium followed by hysterectomy. The operation performed in most instances has been complete abdominal hysterectomy with removal of both tubes and ovaries and a small segment of vagina. In a few cases the broad ligaments have been explored with removal of iliac nodes. The parametrial tissues removed have been somewhat more extensive than in the ordinary simple hysterectomy, but the operation in question cannot be considered to be of a radical type upon the order of the Wertheim procedure.

Five-year results for each method of treatment are shown in Table 1. The highest rate of survival occurs in the group treated by surgery alone without evidence of superiority for the combined treatment. It should be noted, however, that selectivity inherent in any program of therapy, and the absence in such over-all results of data upon other clinical factors, mitigates against validity of apparent values. It was therefore decided to re-evaluate the results of therapy dependent on several important clinical features.

Since the relative size of the uterus has been shown to be of definite prognostic value, it is deemed practical to evaluate the results on that basis. A modified form of the Healy and Brown classification is used for dividing the patients into appropriate groups. Data are taken from clinical records, and patients with uteri of a size smaller than that of a 2½-month pregnancy, or sounding less than 12.0 cm. in depth, are grouped as "early cases." Those of larger dimensions, or with evidence of extension outside the uterus regardless of size, are considered as "advanced cases." Results of that comparison are shown in Table 2, and a better survival rate can be seen for the early cases regardless of the type of treatment applied. Preoperative irradiation is not

shown to produce any significant improvement among early cases, but an improvement in results can be seen for that procedure among advanced cases. From those data it can be stated that preoperative irradiation should be employed in patients suited to hysterectomy who present enlarged uteri, or evidence of spread outside the uterus.

are correlated with type of treatment, and the clinical results given in Table 3. For the patients in question the degree of differentiation is shown to affect strongly the prognosis in corpus cancer. Without regard to the type of treatment applied it can be seen that the ratio of survival for well differentiated lesions is almost 2:1 that of undif-

TABLE 1.—TABLE SHOWING THE 5-YEAR-SURVIVAL RATE FROM THREE DIFFERENT TECHNIQUES OF TREATMENT.

ADENOCARCINOMA OF CORPUS UTERI

	Treated		*5-Year Survivals*	
Treatment	*No.*	*%*	*No.*	*%*
Radiation Only	112	43.1	29	25.9
Surgery Only	57	21.9	40	70.1
Irradiation and Surgery	91	35	66	72.5
Totai	260	100	135	50.2

TABLE 2.—TABLE ILLUSTRATING THE EFFECT OF SIZE OF UTERUS ON THE 5-YEAR-SURVIVAL RATE BY THREE DIFFERENT TECHNIQUES OF TREATMENT.

ADENOCARCINOMA OF CORPUS UTERI

	Early			*Late*		
		5-Year Survivals			*5-Year Survivals*	
Treatment	*Treated No.*	*No.*	*%*	*Treated No.*	*No.*	*%*
Irradiation Alone	51	20	39.2	61	9	14.7
Surgery Alone	45	35	77.7	12	5	41.6
Preoperative Irradiation	52	43	82.7	39	23	59
Total	148	98	66.2	112	37	33.0

There is lack of agreement regarding the significance of tumor differentiation as noted microscopically. For an evaluation of results on that basis, a modification of the Healy and Cutler[2] histological grading as described by Palmer[9] is believed to be the most practical. It is easily applied, and provides a definite selection of cases. Lesions microscopically classified as types I and II are included in the "more differentiated class," and types III and IV in the "less differentiated class." Using that broad histologic grouping the data

ferentiated forms (63.4%:34.6%). The ratio is of about the same value for patients treated by irradiation alone (32.3%:17.0%). A change in values can be seen, however, among patients treated by hysterectomy alone, or in conjuction with preoperative irradiation. Among the patients treated by surgery alone, the ratio of survival of differentiated lesions is 3:1, that of undifferentiated forms (94.1%:34.8%). For the combined treatment the value is changed to 4:3 (80.7%:59.0%).

Specific explanation for the improve-

ment in prognosis shown for preoperative irradiation in patients with undifferentiated tumors cannot be made except upon the basis of natural history. In pursuit of an explanation a review has been made of the patients treated by hysterectomy alone and those given the combined treatment to search for differences in operability. Good comparability is found in age, weight, and associated medical complications. The only exception is to be found in the fact that 12 of the group treated by surgery alone were not diagnosed until after operation. That would indicate early lesions, but as such should tend to advance results in that group. Only 4 of those 12 patients were asymptomatic, however, and there should have been suspicion of cancer in the remaining 8. All of the patients given preoperative irradiation were diagnosed before therapy. Thus we have not found any difference in clinical material that might be expected to result in better survival for patients given the combined treatment. It is believed valid to conclude that preoperative irradiation is essential for lesions that show evidence of anaplasia. Differences in clinical behavior must be a factor of significance, but beyond the vagaries of natural history no definite explanation can be made.

A number of publications have given emphasis to the prognostic value of tumor control manifested by disappearance of cancer in specimens removed after preoperative irradiation. That phenomenon can be seen to apply here in data given in Table 4 which shows the better survival rate for patients presenting no evidence of residual cancer in uteri removed after the application of Roentgen rays and radium. If favorable radiosensitivity of undifferentiated lesions prompts that evidence of control, one might hope to have greater proof of the value of preoperative treatment. In an earlier review upon a lesser number of patients we had, however, been of the opinion that the incidence of tumor disappearance is lower among undifferentiated forms. Analysis of the material here reported shows no significant statistical difference for the per cent of cases histologically controlled in either group. Those data are given in Table 5. Thus we do not find evidence of difference in response to irradiation to explain the improvement in results that follows preoperative irradiation in undifferentiated tumors. One can conclude only that prognosis is affected adversely by lack of differentiation, and that prognosis in those instances can be improved among operable patients by the addition of preoperative irradiation.

TABLE 3.—TABLE ILLUSTRATING THE EFFECT OF HISTOLOGICAL GRADING ON THE 5-YEAR-SURVIVAL RATE BY THREE DIFFERENT TECHNIQUES OF TREATMENT.

ADENOCARCINOMA OF CORPUS UTERI

	Well Differentiated			*Anaplastic*		
		5-Year Survivals			*5-Year Survivals*	
Treatment	*Treated No.*	*No.*	*%*	*Treated No.*	*No.*	*%*
Irradiation Only	65	21	32.3	47	8	17
Surgery Only	34	32	94.1	23	8	34.8
Preoperative Irradiation	57	46	80.7	34	20	59
Total	156	99	63.4	104	36	34.6

Those effects, in addition to the effects of the size of the uterus described above, suggest the possibility for a clinical classification that will more effectively predict prognosis. In Table 6 the patients are grouped in a manner

earlier years radium was applied by means of an intrauterine tandem of fixed length containing only two sources. That linear source was not always equal to the measurement of uterine depth. A third tube was added

TABLE 4.—TABLE ILLUSTRATING THE BENEFICIAL EFFECT OF THE DISAPPEARANCE OF CANCER AT TIME OF OPERATION.

ADENOCARCINOMA OF CORPUS UTERI

Treatment: Preoperative Irradiation and Hysterectomy

	Treated		*5-Year Survivals*	
	No.	*%*	*No.*	*%*
Histologically Controlled	60	65.9	49	81.7
Histologically Uncontrolled	31	34.1	17	54.8
Total	91	100	66	72.5

TABLE 5.—TABLE ILLUSTRATING THE RELATIVE RADIOSENSITIVITY OF THE TUMOR DEPENDING ON ITS HISTOLOGICAL APPEARANCE.

ADENOCARCINOMA OF CORPUS UTERI

Treatment: Preoperative Irradiation and Hysterectomy

Histological Classification	*Treated No.*	*Histologically Controlled No.*	*%*
Well Differentiated	57	32	56.1
Anaplastic	34	17	50.0
Total	91	49	53.8

TABLE 6.—TABLE ILLUSTRATING THE ARRANGEMENT OF CLINICAL CLASSIFICATIONS TO DEMONSTRATE RELATIVE PROGNOSES.

ADENOCARCINOMA OF CORPUS UTERI

		5-Year Survivals	
Groups	*No.*	*No.*	*%*
I. Early—Well Differentiated	82	69	84.1
II. Early—Anaplastic	66	29	43.9
Advanced—Well Differentiated	74	30	40.5
III. Advanced—Anaplastic	38	7	18.4
Total	260	135	50.2

demonstrating prognosis made upon a combination of those two clinical criteria.

Mention should be made of method of radium treatment. During the period included in this report several different techniques have been employed. In the

at a later date. The method of treatment was subsequently changed to simulate as nearly as possible the packing technique devised by Heyman. The clinical results following the use of an intrauterine tandem, and those following use of multiple capsules are given

in Table 7. Whether treated by irradiation alone, or in conjunction with surgery, the use of multiple capsules shows a better result. That method is especially important for enlarged uteri. Among those of normal or small size the method may be difficult to apply, and the number of tubes that can be introduced into the uterus may be few. In those instances the linear arrangement of an intrauterine tandem adjusted to uterine depth can be an effective method. In more recent years we have added the use of vaginal sources. From that method there should be decrease in incidence of recurrence at the vaginal vault, as well as improvement in distribution of radiation. We believe also that external irradiation should be employed in addition to the radium treatment for operable patients as well as for those to be treated by irradiation alone.

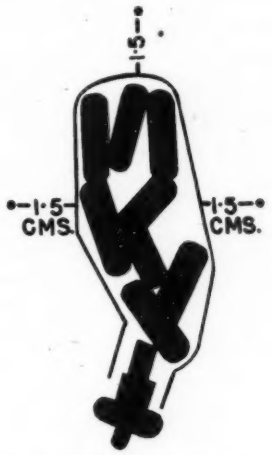
TABLE 7.—TABLE COMPARING THE EFFECT OF MULTIPLE CAPSULES AND TANDEM ON THE SURVIVAL RATE.

ADENOCARCINOMA OF CORPUS UTERI

	Tandem			*Multiple Capsules*		
		5-Year Survivals			*5-Year Survivals*	
	Treated No.	No.	%	*Treated* No.	No.	%
Irradiation Alone	43	6	13.9	69	23	33.3
Preoperative Irradiation and then Hysterectomy	19	10	52.6	72	56	77.7
	62	16	25.8	141	79	56.0

The distribution of radium radiation has been studied in a total of 43 patients. Size and shape of the uterus, the presence of fibroids or other tumor masses, and the arrangement of radium tubes affect the amount of radiation arriving at various points. Expression of dose given in milligram-hours gives no indication of biologic results to be expected. Costolow, Nolan, *et al.*[1] employed a point designated as "C" for expressing dose in roentgens. Heyman and Brenner chose a zone 1.5 cm. from the surface of the radium pack. Considerable variation in dose is to be found at different points, no one of which expresses adequately the dose applied. For this study tracings were made of anterio-posterior and lateral radiographs taken during radium treatment. Using standard radium dosage charts it was possible to calculate the roentgens arriving at any one point from any particular capsule. The total dose was calculated by summing together the amounts contributed at any given point from all capsules. Three points were finally considered as the necessary minimum to represent the over-all dose delivered to the tumor. These points were selected on a geographical basis along the midline above the fundus, and on both lateral sides of the uterus. These were located 1.5 cm. distance from the edge of the radium outline as shown in Fig. 1. The cases were then divided into 4 groups depending upon the minimum dose calculated at each of those three points and grouped into doses of 4000 roentgens or less, 4000 to 5500 roentgens, 5500 to 7000, 7000 or more roentgens. Table 8 shows the results according to those categories. It is seen that a progressively better prognosis is obtained when the dosages delivered approach more adequate irradiation. An attempt to define adequate dosages in terms of milligram hours was impossible be-

cause of its dependence on the anatomy present and the distribution of the radium capsules. For the most part, however, the larger the uterus the greater the number of milligram hours necessary to give adequate irradiation. A better indication of the dosage distribution was obtained when the Roentgen ray films and the clinical features were individually considered. Scintillation probe counters now make it possible to obtain measured dosages in the rectum and bladder. If these are also considered it would seem possible to arrive at a relatively safe yet adequate dose to the tumor. Without this meticulous individualization the improvement in clinical results from intrauterine radium implantations is haphazard and often ineffective. It is believed that this is the clue to the difficulty in demonstrating a direct relationship of clinical improvement for the preoperative use of radium or for radiation therapy alone.



Technique of Calculating Dosage

Fig. 1.—Adenocarcinoma of the corpus uteri. The figure illustrates the reference points selected at which to measure the dose of radiation. The minimum and maximum dosages at these three points are considered representative of the dose delivered to the entire uterus.

TABLE 8.—TABLE ILLUSTRATING THE EFFECT OF RADIATION DOSAGE DELIVERED TO THE UTERUS ON THE SURVIVAL RATE.

ADENOCARCINOMA OF CORPUS UTERI

Minimum Roentgens Calculated at 3 Points Around the Uterus	*Treated*	*5-Year Survivals*	
	No.	*No.*	*%*
4000 or less	7	2	28.5
4000 to 5500	17	7	41.2
5500 to 7000	12	8	66.6
7000 or more	7	6	85.7
Total	43	23	53.5

If in the data given in Table 8 one compares results in patients given combined treatment with those treated by irradiation alone, it can be demonstrated that radiation effectively con-

trols endometrial cancer. Review of the 43 cases reveals a satisfactory uniform and adequate dose to have prevailed in 19 cases at the time of the radium application. Twelve of those 19 patients had subsequent hysterectomies, of whom 9 survived 5 years without evidence of disease (75%). Five of the 7 who were treated by irradiation alone survived 5 years (71.4%). Such comparable results speak well for the ability of radiotherapy to cure corpus cancer when properly applied.

Conclusions. 1. Prognosis in corpus cancer is affected adversely by enlargement of the uterus, and by undifferentiation of the tumor.

2. The use of preoperative Roentgen rays and radium will improve prognosis in patients with enlarged uteri suitable for hysterectomy. A more significant improvement in results following preoperative irradiation is found among patients with undifferentiated tumors. No specific explanation is offered for that occurrence.

3. Patients with well differentiated tumors in uteri of normal or small size present an excellent prognosis for treatment by hysterectomy alone. The improvements expected for preoperative irradiation are not demonstrable in that group. Patients with the same clinical criteria but not suited to surgery also present an excellent prognosis provided a suitable distribution of an adequate dose of radiation is attained.

4. Radium treatment should include intrauterine and intravaginal applications. In small uteri of normal contour a linear arrangement of radium tubes adjusted to depth of the uterine space may deliver an adequate intrauterine dose. In all other instances better results will follow the multiple capsule packing technique.

5. Attention to detail and individualization are required in the attempt to arrive at an adequate dose suitably distributed throughout the tumor bearing region. That is not attainable in every instance.

6. Hysterectomy should be employed in all operable patients. Where preoperative irradiation is applied, the disappearance of recognizable tumor in the removed specimen presents a favorable prognostic sign.

Summary. The literature dealing with clinical aspects and causative factors in adenocarcinoma of the uterine corpus is reviewed. Discussion is given the status of radiotherapy used alone or in conjunction with surgery. Clinical experience is reported for an 18-year period at the Barnes and the Barnard Free Skin and Cancer Hospitals. An attempt is made to explain the indefiniteness that may be apparent in search of evidence of improvement in clinical results following the use of preoperative irradiation. The review of published data and the study of clinical experience is believed to present evidence that improvement in therapeutic results necessitates more adequate irradiation and greater individualization in selection of method of treatment for each patient.

REFERENCES

(1) **Costolow, W. E., Nolan, J. F., Budenz, G. C.,** and **Dusault, L.:** Am. J. Roent. Rad. Ther. & Nucl. Med., **71**, 669, 1954.
(2) **Healy, W. R.,** and **Cutler, M.:** Am. J. Obst. & Gynec., **19**, 457, 1930. (3) **Henriksen, E.:** Am. J. Obst. & Gynec., **58**, 924, 1949. (4) **Heyman, J.:** Acta radiol., **22**, 11, 1941. (5) **Heyman, J.:** Acta radiol., **27**, 328, 1946.
(6) **Javert, C. T.:** Am. J. Obst. & Gynec., **64**, 780, 1952.
(7) **Larson, J. A.:** Obst. & Gynec., **3**, 551, 1954.
(8) **Novak, E.:** Textbook of Gynecology. 3rd ed. Baltimore: Williams & Wilkins Co., 1948.
(9) **Palmer, J. P., Reinhard, M. C., Sadugor, M. G.,** and **Goltz, H. L.:** Am. J. Obst. & Gynec., **58**, 457, 1949.

INDEX

A

Abdominal aortography, 586
Abelmann, W. H., *see* Kowalski, H. J., *et al.*, 622
Absence, congenital, of main branch of pulmonary artery, 673
Acidosis and uremia due to advanced renal disease, uptake of base in, 656
ACTH and compounds E and F in idiopathic thrombocytopenic purpura, 1
Addison's disease and active pulmonary tuberculosis, treatment of coexisting, 491
Adenomas, multiple, of parathyroids and pancreatic islets, concomitance of, with tumor of the pituitary: syndrome with familial incidence, 190
Adrenergic blocking agent, Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyl] piperazine), effects of intravenous infusions of optical isomers of, upon hypertensive subjects, 614
Adrenocorticotropic hormone, *see* ACTH
Aerosols, citric acid, experimental production of cough induced by; evaluation of antitussive agents, 156
Age, effect of, on protein concentration of cerebrospinal fluid of "normal" individuals and patients with poliomyelitis and other diseases, 510
Alexander, J. D., Jr., *see* Weiss, W., *et al.*, 148
Amebicidal, synergistic, effect of tetracycline, oxytetracycline and carbomycin on cultures of *Endameba histolytica*, 16
Amyloidosis, primary systemic, 317
complicating rheumatoid arthritis, 554
Anorexia, irritability and convulsions: evidence of subdural hematomy in infancy, 540
Antagonists, opiate, nalorphine and levallorphan, 456
Antibiotics, eleven, and sulfadiazine, *in vitro* susceptibility of meningococci to, 534
Antibody, capacity of seriously wounded patients to produce, 251
Anticoagulant, circulating antithromboplastic: ineffectiveness of cortisone and corticotropin, 269
therapy in acute myocardial infarction, selection of patients for, 133
Anti-emetic chlorpromazine, clinical studies of, 174
Antithromboplastic anticoagulant, circulating: ineffectivness of cortisone and corticotropin, 269
Antitussive agents, evaluation of; experimental production of cough induced by citric acid aerosols, 156
Aortic tortuosity, value of lateral ballistocardiograms in differentiating, from myocardial dysfunction, 125
Aortography, abdominal, 586
Apresoline (l-hydrazinophthalazine) in management of hypertension appearing early in pregnancy, 140
Arfonad, long-term intravenous use of, in pulmonary edema, 626
Arneson, A. N., *see* Sherman, A. I., 701
Aronovitch, M., *see* Browne, J. S. L., *et al.*, 491
Arteriosclerotic, hypertensive, syndrome, reserpine in, 560
Artery, pulmonary, congenital absence of main branch of, 673
Arthritis, rheumatoid, amyloidosis complicating, 554
Atelectasis, therapy and prevention of, use of trypsin or streptokinase-streptodornase for, 432

B

Babbott, F. L., Jr., and Gordon, J. E., Modern measles, 334
Ballistocardiograms, lateral, value of, in differentiating aortic tortuosity from myocardial dysfunction, 125
Barach, A. L., *see* Bickerman, H. A., *et al.*, 156
Beck, J. C., *see* Browne, J. S. L., *et al.*, 491
Beerman, H., and Mitchell, G. H., Nodular vasculitis, 469
Beizer, L. H., *see* Steinfield, E., 388
Bellet, S., *see* Kramer, L. B., *et al.*, 614
see Lechner, E., *et al.*, 282
Benda, C. E., Maletskos, C. J., Hutchinson, J. C., and Thomas E. B., Thyroid function in myotonia dystrophica 668
Benemid (probenecid), effect of, on phosphate excretion and other metabolic processes, 256
Bergendahl, E., *see* Seneca, H., 16
Bergy, G. C., *see* Waddington, W. S., *et al.*, 164
Bickerman, H. A., Barach, A. L., Itkin, S., and Drimmer, F., Experimental production of cough in human subjects induced by citric acid aerosols: evaluation of antitussive agents, 156
Bierman, H. R., *see* Coblentz, A., *et al.*, 298

Blocking agent, adrenergic, Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyl] piperazine), effects of intravenous infusions of optical isomers of, upon hypertensive subjects, 614
Blood and urine, levels of agents in: control of hypertension by hyphex, 405
cell, red, in health and certain hematologic disorders, radioactive sodium chromate to evaluate life span of, 40
coagulation, lack of effect of fat ingestion on, 652
portal and hepatic venous, microbiologic studies of, in man, 298
pressure reduction with phenoxybenzamine (Dibenzyline-688A), cerebral hemodynamic response to, 563
Bock, D. G., *see* Havens, W. P., Jr., *et al.*, 251
Browne, D. C., *see* Welch, G. E., *et al.*, 643
Browne, J. S. L., Aronovitch, M., Beck, J. C., Leith, W., and Meakins, J. F., Treatment of coexisting Addison's disease and active pulmonary tuberculosis, 491
Bruce, R. A., *see* Pampush, J. J., 605
Burchenal, J. H., Karnofsky, D. A., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, C. T. C., Mermann, A. C., Yuceoglu, M., and Rhoads, C. P., Clinical evaluation of 6-mercaptopurine in leukemia, 371
Burns, J. J., *see* Weiner, M., *et al.*, 36

C

Carbomycin, tetracycline and oxytetracycline, synergistic amebicidal effect of, on cultures of *Endameba histolytica*, 16
Carbonic anhydrase inhibitor, satisfactory use of, as oral diuretic, 214
Carcinoma of endometrium, 701
metastatic, of liver, hepatic tests in, 312
Cardiac enlargement following mitral commissurotomy, 57
output of normal subjects determined by dye-injection method at rest and during exercise, 622
Cardillo, T. E., Mullin, E. W., Schiffer, L. M., and Lyons, R. H., Satisfactory use of carbonic anhydrase inhibitor as oral diuretic, 214
Cardiospasm, 218
and gastroesophageal reflux, normal function and role of gastroesophageal vestibule in, 417
Cardiovascular studies during upper respiratory tract infection, 275
Cary, S. K., *see* Zarafonetis, C. J. D., *et al.*, 1
Cerebral hemodynamic response to blood pressure reduction with phenoxybenzamine (Dibenzyline-688A), 563
Cerebrospinal fluid of "normal" individuals and patients with poliomyelitis and other diseases, effect of age on protein concentration of, 510
Chambers, W. R., Anorexia, irritability and convulsions: evidence of subdural hematoma in infancy, 540
Chenkin, T., *see* Weiner, M., *et al.*, 36
Childs, B., Genetics in pediatric disease, 680
Chlorpromazine, anti-emetic, clinical studies of, 174
Cholerae suis, Salmonella, 525
Chorea, Huntington's, oral procaine amide in, 70
Citric acid aerosols, experimental production of cough induced by; evaluation of antitussive agents, 156
serum, in Paget's disease, 301
Cliffton, E. E., Present status of therapeutic use of enzymes, 568
Clotting activity of human erythrocytes, 207
Coagulation, blood, lack of effect of fat ingestion on, 652
Coblentz, A., Kelly, K. H., Fitzpatrick, L., and Bierman, H. R., Microbiologic studies of portal and hepatic venous blood in man, 298
Colville, V. F., *see* Zarafonetis, C. J. D., 461
Commissurotomy, mitral, cardiac enlargement following, 57
Complement components in sera and urines of patients with severe proteinurias, 448
loss, site of, in experimental glomerulonephritis, 454
Compounds E and F, and ACTH in idiopathic thrombocytopenic purpura, 1
Congenital absence of main branch of pulmonary artery, 673
Convulsions, anorexia and irritability: evidence of subdural hematoma in infancy, 540
Coronary occlusion and infarction, association of, with diabetes mellitus: necropsy study, 53
Corticotropin and cortisone, ineffectiveness of: circulating antithromboplastic anticoagulant, 269
Cortisone and corticotropin, ineffectiveness of: circulating antithromboplastic anticoagulant, 269
Cough, experimental production of, induced by citric acid aerosols: evaluation of antitussive agents, 156
Craighead, C. C., *see* Welch, G. E., *et al.*, 643

D

Daly, J. W., Diuretic effect and local tolerance of new type of mercurial rectal suppository, 440
Danzig, L. E., and Gomez, A. C., Long-term intravenous use of Arfonad in pulmonary edema, 626
de Andino, A. M., Jr., *see* Torregrosa, M. V., *et al.*, 269
DeMyer, W., and Dyken, M., Oral procaine amide in Huntington's chorea, 70
Dennis, E., *see* Hughes, W., *et al.*, 21
Diabetes mellitus, association of coronary occlusion and infarction with; necropsy study, 53
Diagnosis of hyperparathyroidism, measurement of per cent renal phosphorus reabsorption in, 262
Diaz Rivera, R. S., *see* Torregrosa, M. V. *et al.*, 269
Dibenzyline-688A (phenoxybenzamine), cerebral hemodynamic response to blood pressure reduction with, 563
Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyl] piperazine), an adrenergic blocking agent, effects of intravenous infusions of optical isomers of, upon hypertensive subjects, 614
Diuretic effect and local tolerance of new type of mercurial rectal suppository, 440
oral, satisfactory use of carbonic anhydrase inhibitor as, 214
Dizon, M., *see* Moyer, J. H., *et al.*, 174
Dock, W., Value of lateral ballistocardiograms in differentiating aortic tortuosity from myocardial dysfunction, 125
Dowling, H. F., *see* Kofman, S., *et al.*, 426, 432
Drake, F. R., Drug therapy of Parkinson's syndrome, 97
Drimmer, F., *see* Bickerman, H. A., *et al.*, 156
Drug therapy of Parkinson's syndrome, 97
Dunsmore, L., *see* Neubauer, R. A., *et al.*, 306
Dye-injection method, cardiac output of normal subjects determined by, at rest and during exercise, 622
Dyken, M., *see* DeMyer, W., 70

E

E and F, compounds, and ACTH in idiopathic thrombocytopenic purpura, 1
Eckenhoff, J. E., and Funderburg, L. W., Use of opiate antagonists nalorphine and levallorphan, 546
Edema, pulmonary, long-term intravenous use of Arfonad in, 626
Eisenberg, G. M., *see* Weiss, W., *et al.* 148
Electrocardiographic pattern changes, serial, occurring with two sequential anterior myocardial infarctions, 288
Electrolytes, serum and muscle, study of: comparison of tolerance of normal dog and dog with myocardial infarction to organic mercurial (Mercurophylline), 282
Ellis, L. B., *see* Kowalski, H. J., *et al.*, 622
Ellison, R. R., *see* Burchenal, J. H., *et al.*, 371
Elwood, M. J., *see* Müller, O. H., *et al.*, 510
Emmett, R., *see* Welch, G. E., *et al.*, 643
Endameba histolytica, cultures of, synergistic amebicidal effect of tetracycline, oxytetracycline and carbomycin on, 16
Endometrium, carcinoma of, 701
Enzymes, present status of therapeutic use of, 568
proteolytic, effect of, on physical and chemical characteristics of tracheobronchial secretions of patients with poliomyelitis, 426
Erythrocytes and leukocytes, human, sulfhydryl content of, 73
human, clotting activity of, 207
sheep, Forssman-like behavior of cold hemagglutinins for, 461
Excretion, phosphate, and other metabolic processes, effect of probenecid (Benemid) on, 256
sodium, in advanced renal disease, 306
Exercise and at rest, cardiac output of normal subjects determined by dye-injection method during, 622
tolerance, natural history and functional capacity of unoperated patients with mitral stenosis, 605

F

F and E compounds, and ACTH in idiopathic thrombocytopenic purpura, 1
Fabricant, N. D., Recent trends in nasal medication, 465
Familial incidence, syndrome with: concomitance of multiple adenomas of parathyroids and pancreatic islets with tumor of pituitary, 190
Fanconi syndrome and its clinical variants, 378
Fat ingestion, lack of effect of, on blood coagulation, 652
Fazekas, J. F., *see* Kleh, J., 560
Febrile illnesses, evaluation of anamnestic serum reaction in certain, 520
Feldman, M., Incidence of perforation in benign peptic ulcer of greater curvature of stomach, 506
and Feldman, M., Jr., Association of coronary occlusion and infarction with diabetes mellitus: necropsy study, 53

Feldman, M., Jr., *see* Feldman, M., 53
Finland, M., *see* Love, B. D., Jr., 534
Finnerty, F. A., Jr., l-Hydrazinophthalazine (Apresoline) in management of hypertension appearing early in pregnancy, 140
Fitzpatrick, L., *see* Coblentz, A., *et al.*, 298
Flack, H. A., Mart, J. A., and Maher, C. C., Serial electrocardiographic pattern changes occurring with two sequential anterior myocardial infarctions, 288
Flippin, H. F., *see* Weiss, W., *et al.*, 148
Flynn, J. E., Siebens, A. A., and Williams, S. F., Congenital absence of main branch of pulmonary artery, 673
Follette, J. H., *see* Hardin, B., *et al.*, 73
Ford, R., *see* Hughes, W., *et al.*, 21
Ford, R. V., *see* Spurr C. L., *et al.*, 256
Forssman-like behavior of cold hemagglutinins for sheep erythrocytes, 461
Frank, N. R., *see* Kowalski, H. J., *et al.*, 622
Function, thyroid, in myotonia dystrophica, 668
Functional capactiy, natural history and exercise tolerance of unoperated patients with mitral stenosis, 605
Funderburg, L. W., *see* Eckenhoff, J. E., 546

G

Gardner, F. H., *see* Read, R. C., *et al.*, 40
Garrigues, E., *see* Neubauer, R. A., *et al.*, 306, 656
Garson, E., *see* Spurr, C. L., *et al.*, 256
Gastric secretion and stress in man: mechanisms involved in insulin hypoglycemia, 630
Gastroesophageal reflux and cardiospasm, normal function and role of gastroesophageal vestibule in, 417
vestibule, normal function and role in cardiospasm and gastroesophageal reflux, 417
Genetics in pediatric disease, 680
Georgatsos, J. G., *see* Quick, A. J., *et al.*, 207
Glomerulonephritis, experimental, site of complement loss in, 454
Goldstein, G. S., *see* Perry, H. M., Jr., *et al.*, 396, 405
Gomez, A. C., *see* Danzig, L. E., 626
Gordon, J. E., *see* Babbott, F. L., Jr., 334
Gottlieb, H., *see* Seven, M. J., *et al.*, 646
Gould, D. M.,, and Willson, J. K. V., Abdominal aortography, 586

H

Hardin, B., Valentine, W. N., Follette, J. H., and Lawrence, J. S., Sulfhydryl content of human leukocytes and erythrocytes, 73
Harris, R. S., *see* Kowalski, H. J., *et al.*, 275
Havens, W. P., Jr., Bock, D. G., and Siegel, I., Capacity of seriously wounded patients to produce antibody, 251
Health and certain hematologic disorders, radioactive sodium chromate to evaluate life span of red blood cell in, 40
Hemagglutinins, cold, Forssman-like behavior of, for sheep erythrocytes, 461
Hematologic disorders, certain, and health, radioactive sodium chromate to evaluate life span of red blood cell in, 40
Hematoma, subdural, in infancy: anorexia, irritability and convulsions, evidence of, 540
Hemochromatosis, N-hydroxyethylethylenediamine triacetic acid, Versenol, in, 646
Hemodynamic, cerebral, response to blood pressure reduction with phenoxybenzamine (Dibenzyline-688A), 563
Hepatic and portal venous blood in man, microbiologic studies of, 298
disease, metabolic transformation and effects of phenylbutazone in, 36
tests in metastatic carcinoma of liver, 312
venule and portal venous system in man, simultaneous pressure measurements in, 643
History, natural, functional capacity and exercise tolerance of unoperated patients with mitral stenosis, 605
Hoeffler, G., *see* Welch, G. E., *et al.*, 643
Holt, C. J., Cardiospasm, 218
Hughes, W., Dennis, E., McConn, R., Ford, R., and Moyer, J. H., Reserpine (Serpasil) in hypertension, 21
Hunt, J. S., Pathogenesis of infectious mononucleosis, 83
Huntington's chorea, oral procaine amide in, 70
Hussey, C. V., *see* Quick, A. J., *et al.*, 207
Hutchinson, J. C., *see* Benda, C. E., *et al.*, 668
l-Hydrazinophthalazine (Apresoline) in management of hypertension appearing early in pregnancy, 140
pharmacological and chemical observations on: control of hypertension by hyphex, 396
Hyperparathyroidism, measurement of per cent renal phosphorus reabsorption in diagnosis of, 262
Hypertension appearing early in pregnancy, l-hydrazinophthalazine (Apresoline) in management of, 140
control of, by hyphex: Pharmacological and chemical observations on l-hydrazinophthalazine, 396
control of, by hyphex: Levels of agents in urine and blood, 405
reserpine (Serpasil) in, 21

Hypertensive arteriosclerotic syndrome, reserpine in, 560
subjects, effects of intravenous infusions of optical isomers of Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyll piperazine), upon, 614
Hyphex, control of hypertension by: pharmacological and chemical observations on l-hydrazinophthalazine, 396
control of hypertension by: levels of agents in urine and blood, 405
Hypoglycemia, insulin, mechanisms involved in: stress and gastric secretion in man, 630

I

Incidence, familial, syndrome with: concomitance of multiple adenomas of parathyroids and pancreatic islets with tumor of pituitary, 190
Infancy, subdural hematoma in; anorexia, irritability and convulsions, evidence of, 540
Infarction and occlusion, coronary, association of, with diabetes mellitus: necropsy study, 53
acute myocardial, selection of patients for anticoagulant therapy in, 133
myocardial, comparison of tolerance of normal dog and dog with, to organic mercurial (Mercurophylline): study of serum and muscle electrolytes, 282
Infarctions, myocardial, two sequential anterior, serial electrocardiographic pattern changes occurring with, 288
Infection, upper respiratory tract, cardiovascular studies during, 275
Infectious mononucleosis, pathogenesis of, 83
Infusions, intravenous, effects of, of optical isomers of Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyl] piperazine), an adrenergic blocking agent, upon hypertensive subjects, 614
Ingelfinger, F. J., Kramer, P., and Sanchez, G. C., Gastroesophageal vestibule, normal function and role in cardiospasm and gastroesophageal reflux, 417
Ingestion, fat, lack of effect of, on blood coagulation, 652
Inhibitor, satisfactory use of carbonic anhydrase, as oral diuretic, 214
Insulin hypoglycemia, mechanisms involved in: stress and gastric secretion in man, 630
Irritability, anorexia and convulsions: evidence of subdural hematoma in infancy, 540
Israel, H. L., *see* Seven, M. J., *et al.*, 646
Itkin, S., *see* Bickerman, H. A., *et al.*, 156

J

Jackson, G. C., *see* Kofman, S., *et al.*, 426, 432
Jaworski, A. A., *see* Müller, O. H., *et al.*, 510

K

Karnofsky, D. A., *see* Burchenal, J. H., 371
Kelly, K. H., *see* Coblentz, A., *et al.*, 298
Kent, B., *see* Moyer, J. H., *et al.*, 174
Kirby, W. M. M., *see* Waddington, W. S., *et al.*, 164
Kissin, B., and Kreeger, N., Serum citric acid in Paget's disease, 301
Klebsiella pulmonary disease, 148
Kleh, J., and Fazekas, J. F., Reserpine in hypertensive arteriosclerotic syndrome, 560
Knight, R. W., *see* Moyer, J. H., *et al.*, 174
Koelle, G. B., *see* Kramer, L. B., *et al.*, 614
Kofman, S., Lepper, M. H., Jackson, G. G., and Dowling, H. F., Effect of proteolytic enzymes on physical and chemical characteristics of tracheobronchial secretions of patients with poliomyelitis, 426
Use of trypsin or streptokinase-streptodornase for therapy and prevention of atelectasis, 432
Koomen, J., Jr., and Morgan, H. R., Evaluation of anamnestic serum reaction in certain febrile illnesses, 520
Kowalski, H. J., Abelmann, W. H., McNeely, W. F., Frank, N. R., and Ellis, L. B., Cardiac output of normal subjects determined by dye-injection method at rest and during exercise, 622
Rutstein, D. D., Reynolds, W. E., Harris, R. S., and Shoulberg, J. M., Cardiovascular studies during upper respiratory tract infection in normal subjects, 275
Kramer, L. B., Van Horne, R., Bellet, S., and Koelle, G. B., Effects of intravenous infusions of optical isomers of Dibozane (McN-181; 1,4-Bis[1,4-Benzodioxan-2Ylmethyl] piperazine), an adrenergic blocking agent, upon hypertensive subjects, 614
Kramer, P., *see* Ingelfinger, F. J., *et al.*, 417
Kreeger, N., *see* Kissin, B., 301
Kyle, L. H., *see* Schaaf, M., 262

L

Lange K., and Wenk, E. J., Complement components in sera and urines of patients with severe proteinurias, 448
Site of complement loss in experimental glomerulonephritis, 454
Lawrence, J. S., *see* Hardin, B., *et al.*, 73
Lechner, E., Nunez, H., Nemir, P., Jr., and Bellet, S., Comparison of tolerance of normal dog and dog with myocardial infarction to organic mercurial (Mercurophylline); study of serum and muscle electrolytes, 282

Leith, W., *see* Browne, J. S. L., *et al.*, 491
Lepper, M. H., *see* Kofman, S., *et al.*, 426, 432
Lesions of retina and optic nerve secondary to distant trauma, 226
Leukemia, 6-mercaptopurine in treatment of, 371
Leukocytes and erythrocytes, human, sulfhydryl content of, 73
Levallorphan and nalorphine, use of opiate antagonists, 546
Liver, metastatic carcinoma of, hepatic tests in, 312
Love, B. D., Jr., and Finland, M., *In vitro* susceptibility of meningococci to eleven antibiotics and sulfadiazine, 534
Lyons, R. H., *see* Cardillo, T. E., *et al.*, 214

M

Magee, J., *see* Neubauer, R. A., *et al.*, 306
Maher, C. C., *see* Flack, H. A., *et al.*, 288
Maletskos, C. J., *see* Benda, C. E., *et al.*, 668
Manning, P. R., and Walford, R. L., Lack of effect of fat ingestion on blood coagulation, 652
Mart, J. A., *see* Flack, H. A., *et al.*, 288
Mathews, W. H., Primary systemic amyloidosis, 317
McConn, R., *see* Hughes, W., *et al.*, 21
McNeely, W. F., *see* Kowalski, H. J., *et al.*, 622
Meakins, J. F., *see* Browne, J. S. L., *et al.*, 491
Measles, modern 334
Measurement of per cent renal phosphorus reabsorption in diagnosis of hyperparathyroidism, 262
Medication, nasal, recent trends in, 465
Menhard, E. M., *see* Perry, H. M., Jr., *et al.*, 396
Meningococci, *in vitro* susceptibility of, to eleven antibiotics and sulfadiazine, 534
6-Mercaptopurine in treatment of leukemia, 371
Mercurial, organic (Mercurophylline), comparison of tolerance of normal dog and dog with myocardial infarction to: study of serum and muscle electrolytes, 282
rectal suppository, diuretic effect and local tolerance of new type of, 440
Mercurophylline, organic mercurial, comparison of tolerance of normal dog and dog with myocardial infarction to: study of serum and muscle electrolytes, 282
Mermann, A. C., *see* Burchenal, J. H., *et al.*, 371
Metabolic processes, other, and phosphate excretion, effect of probenecid (Benemid) on, 256
transformation and effects of phenylbutazone in hepatic disease, 36
Metaplasia, myeloid, as sequela of polycythemia, 388
Metastatic carcinoma of liver, hepatic tests in, 312
Method, dye-injection, cardiac output of normal subjects determined by, at rest and during exercise, 622
Microbiologic studies of portal and hepatic venous blood in man, 298
Miller, S. I., *see* Moyer, J. H., *et al.*, 563
Mitchell, G. H., *see* Beerman, H., 469
Mitral commissurotomy, cardiac enlargement following, 57
stenosis, natural history, functional capacity and exercise tolerance of unoperated patients with, 605
Moldawer, M. P., Nardi, G. L., and Raker, J. W., Concomitance of multiple adenomas of parathyroids and pancreatic islets with tumor of pituitary: syndrome with familial incidence, 190
Mononucleosis, infectious, pathogenesis of, 83
Morgan, H. R., *see* Koomen, J., Jr., 520
Morris, G., *see* Moyer, J. H., *et al.*, 174
Morrow, J. D., *see* Perry, H. M., Jr., *et al.*, 405
Moyer, J. H., Kent, B., Knight, R. W., Morris, G., Dizon, M., Rogers, S., and Spurr, C., Clinical studies of an anti-emetic agent, chlorpromazine, 174
Snyder, H., Miller, S. I., and Smith, C. P., Cerebral hemodynamic response to blood pressure reduction with phenoxybenzamine (Dibenzyline-688A), 563
see Hughes, W., *et al.*, 21
see Spurr, C. L., *et al.*, 256
Müller, O. H., Jaworski, A. A., Silverman, A. C., and Elwood, M. J., Effect of age on protein concentration of cerebrospinal fluid of "normal" individuals and patients with poliomyelitis and other diseases, 510
Mullin, E. W., *see* Cardillo, T. E., *et al.*, 214
Murphy, M. L., *see* Burchenal, J. H., *et al.*, 371
Muscle and serum electrolytes, study of: comparison of tolerance of normal dog and dog with myocardial infarction to, organic mercurial (Mercurophylline), 282
Myeloid metaplasia as sequela of polycythemia. 388
Myerson, R. M., and Pastor, B. H., Fanconi syndrome and its clinical variants, 378
Myocardial dysfunction, value of lateral ballistocardiograms in differentiating aortic tortuosity from, 125

Myocardial infarction, acute, selection of patients for anticoagulant therapy in, 133
infarction, comparison of tolerance of normal dog and dog with, to organic mercurial (Mercurophylline): study of serum and muscle electrolytes, 282
infarctions, two sequential anterior, serial electrocardiographic pattern changes occurring with, 288
Myotonia dystrophica, thyroid function in, 668

N

Nalorphine and levallorphan, use of opiate antagonists, 546
Nardi, G. L., *see* Moldawer, M. P., *et al.*, 190
Nasal medication, recent trends in, 465
Nemir, P., Jr., *see* Lechner, E., *et al.*, 282
Neubauer, R. A., Uptake of base in uremia and acidosis due to advanced renal disease, 656
Magee, J., Dunsmore, L., and Garrigues, E., Sodium excretion in advanced renal disease, 306
N-hydroxyethylethylenediamine triacetic acid, Versenol, in hemochromatosis, 646
Nielsen, R. L., *see* Waddington, W. S., *et al.*, 164
Nodular vasculitis, 469
Nunez, H., *see* Lechner, E., *et al.*, 282

O

Occlusion and infarction, coronary, association of, with diabetes mellitus: necropsy study, 53
Opiate antagonists, nalorphine and levallorphan, use of, 546
Optic nerve and retina, lesions of, secondary to distant trauma, 226
Oxytetracycline, tetracycline and carbomycin, synergistic amebicidal effect of, on cultures of *Endameba histolytica*, 16

P

Paget's disease, serum citric acid in, 301
Pampush, J. J., and Bruce, R. A., Natural history, functional capacity and exercise tolerance of unoperated patients with mitral stenosis, 605
Pancreatic islets and parathyroids, concomitance of multiple adenomas of, with tumor of the pituitary: syndrome with familial incidence, 190
Parathyroids and pancreatic islets, concomitance of multiple adenomas of, with tumor of the pituitary: snydrome with familial incidence, 190
Parkinson's syndrome, drug therapy of, 97
Pastor, B. H., *see* Myerson, R. M., 378
Pathogenesis of infectious mononucleosis, 83
Pediatric disease, genetics in, 680
Peptic ulcer, benign, of greater curvature of stomach, incidence of perforation in, 506
Perforation in benign peptic ulcer of greater curvature of stomach, incidence of, 506
Perry, H. M., Jr., Schroeder, H. A., Goldstein, G. S., and Menhard, E. M., Control of hypertension by hyphex: pharmacological and chemical observations on l-hydrazinophthalazine, 396
Schroeder H. A., Morrow, J. D., and Goldstein, G. S., Control of hypertension by hyphex: levels of agents in urine and blood, 405
Phenoxybenzamine (Dibenzyline-688A), cerebral hemodynamic response to blood pressure reduction with, 563
Phenylbutazone in hepatic disease, metabolic transformation and effects of, 36
Phosphate excretion and other metabolic processes, effect of probenecid (Benemid) on, 256
Phosphorus reabsorption, renal, measurement of per cent, in diagnosis of hyperparathyroidism, 262
Physiological Society of Philadelphia, Proceedings of, 112, 362
Pituitary, tumor of, concomitance of multiple adenomas of parathyroids and pancreatic islets with: syndrome with familial incidence, 190
Poliomyelitis, effect of proteolytic enzymes on physical and chemical characteristics of tracheobronchial secretions of patients with, 426
and other diseases, effect of age on protein concentration of cerebrospinal fluid in "normal" individuals and patients with, 510
Polycythemia, myeloid metaplasia as sequela of, 388
Pons, E., Jr., *see* Torregrosa, M. V., *et al.*, 269
Portal and hepatic venous blood in man, microbiologic studies of, 298
venous system and hepatic venule in man, simultaneous pressure measurements in, 643
Pregnancy, hypertension appearing early in, l-hydrazinophthalazine (Apresoline) in management of, 140
Pressure, blood, reduction with phenoxybenzamine (Dibenzyline-688A), cerebral hemodynamic response to, 563
measurements, simultaneous, in hepatic venule and portal venous system in man, 643

Probenecid (Benemid), effect of, on phosphate excretion and other metabolic processes, 256
Procaine amide, oral, in Huntington's chorea, 70
Protein concentration, effect of age on, of cerebrospinal fluid of "normal" individuals and patients with poliomyelitis and other diseases, 510
Proteinurias, severe, complement components in sera and urines of patients with, 448
Pulmonary artery, congenital absence of main branch of, 673
disease, Klebsiella, 148
edema, long-term intravenous use of Arfonad in, 626
tuberculosis, active, and Addison's disease, treatment of coexisting, 491
Purpura, idiopathic thrombocytopenic, compounds E and F, and ACTH in, 1

Q

Quick, A. J., Georgatsos, J. G., and Hussey, C. V., Clotting activity of human erythrocytes, 207

R

Radioactive sodium chromate to evaluate life span of red blood cell in health and certain hematologic disorders, 40
Raker, J. W., *see* Moldawer, M. P., *et al.*, 190
Ramos-Morales, F., *see* Torregrosa, M. V., *et al.*, 269
Reaction, anamnestic serum, evaluation of, in certain febrile illnesses, 520
Read, R. C., Wilson, G. W., and Gardner, F. H., Use of radioactive sodium chromate to evaluate life span of red blood cell in health and certain hematologic disorders, 40
Rectal suppository, mercurial, diuretic effect and local tolerance of new type of, 440
Red blood cell in health and certain hematologic disorders, radioactive sodium chromate to evaluate life span of, 40
Reece, J. M., and Reynolds, T. B., Amyloidosis complicating rheumatoid arthritis, 554
Reflux, gastroesophageal, and cardiospasm, normal function and role of gastroesophageal vestibule in, 417
Reinhold, J. G., *see* Seven, M. J., *et al.*, 646
Renal disease, advanced, sodium excretion in, 306
advanced, uptake of base in uremia and acidosis due to, 656
phosphorus reabsorption, measurement of per cent, in diagnosis of hyperparathyroidism, 262
Reserpine (Serpasil) in hypertension, 21
in hypertensive arteriosclerotic syndrome, 560
Respiratory tract infection, upper, cardiovascular studies during, 275
Rest and during exercise, cardiac output of normal subjects determined by dye-injection method at, 622
Retina and optic nerve, lesions of, secondary to distant trauma, 226

Reviews (Reviewers' initials in parentheses):

Abramson, H. A. (Ed.), Problems of Consciousness (O. E.), 603
Adler, F. H., Physiology of the Eye, 2nd ed. (G.G.), 116
Altschule, M. D., Physiology in Diseases of the Heart and Lungs (E. K.), 246
Ames, L., B., and Learned, J. Rorschach Responses in Old Age (F. K.), 242
Bauer, L. H. (Ed.), 75 Years of Medical Progress (R. K.), 602
Becker, P. E., Dystrophia Musculorum Progressiva (M. M.), 118
Beeson, P. B., Muschenheim, C., Castle, W. B., Harrison, T. R., Eusterman, G. B., and Williams, R. H. (Eds.), Year Book of Medicine, 1953–1954 (C. Z.), 120
Behnke, A. R., The Relation of Lean Body Weight to Metabolism and Some Consequent Systematizations (W. S.), 249
Bergler, E., and Kroger, W. S., Kinsey's Myth of Female Sexuality (J. W.), 240
Birch, C. A. (Ed.), Emergencies in Medical Practice, 3rd ed. (H. B.), 366
Blades, B. (Ed.), Nash's Surgical Physiology, 2nd ed. (E. A.), 367
Bodian, M. (Ed.), Fibrocystic Disease of the Pancreas (C. Z.), 116
Brookhaven Symposia in Biology No. 5, Major Metabolic Fuels (R. H.), 239
Brun, C., Acute Anuria (W. S.), 239
Burch, G. E., Digital Plethysmography (N. L.), 368
Burt, C., The Causes and Treatment of Backwardness (O. E.), 604
Collis, W. R. F. (Ed.), Fanconi and Wallgren's Textbook of Pediatrics (R. H.), 122
Conway, E. J., The Biochemistry of Gastric Acid Secretion (S. K.), 244
Cope, Z. (Ed.), Medical History of the Second World War. Surgery (L. F.), 121
Crossen, R. J., Diseases of Women, 10th ed. (J. W.), 118
Dimond, E. G., Electrocardiography (J. Z.), 243
Elliott, H. C., Textbook of the Nervous System, 2nd ed. (D. K.), 601
Engle, E. T. (Ed.), Pregnancy Wastage (J. W.), 121
Ernsthausen, W., Das elektrische Herzbild (H. R.), 487
Evans, F. T. (Ed.), Modern Practice in Anaesthesia, 2nd ed. (L. K.), 600
Ferrer, M. I. (Ed.), Cold Injury (N. L.), 124
Fildes, P., and Van Heyningen, W. E. (Eds.), The Nature of Virus Multiplication (C. Z.), 243
Fishbein, M. (Ed.), 1954 Medical Progress (J. Z.), 250
Fishberg, A. M., Hypertension and Nephritis, 5th ed. (R. K.), 250

Flechtner, H. J., Gesundheit durch Krankheit, Das Ratsel der Immunitat (R. K.), 489
Fleming, D., William H. Welch and the Rise of Modern Medicine (E. K.), 604
Forsee, J. H., The Surgery of Pulmonary Tuberlosis (R. T.), 601
Franke, H., Phasenkontrast-Hamatologie (C. Z.), 250
Freud, S., On Aphasia (E. S.), 117
Frosch, J., Ross, N., Tarachow, S., and Arlow, J. A. (Eds.), The Annual Survey of Psychoanalysis, Vol. 2 (O. E.), 368
Galdston, I., The Meaning of Social Medicine (E. C.), 487
Galdston, I. (Ed.), Beyond the Germ Theory (W. S.), 489
Garland, J. (Ed.), The Physician and His Practice (R. K.), 603
Gellhorn, E., Physiological Foundations of Neurology and Psychiatry (S. G.), 238
Gertler, M. M., and White, P. D., Coronary Heart Disease in Young Adults (T. D.), 602
Gill, M., Newman, R., and Redlich, F. C., The Initial Interview in Psychiatric Practice (A. H.), 367
Goldman, L. B., Fundamentals of Clinical Cancer (J. B.), 244
Granet, E., Manual of Proctology (L. F.), 603
Gray, H. (Goss, C. M., Ed.), Anatomy of the Human Body, 26th ed. (R. K.), 604
Gray, P., The Microtomist's Formulary and Guide (E. A.), 599
Greenstein, J. P., and Haddow, A. (Eds.), Advances in Cancer Research, Vol. 1 (C. Z.), 118
Grinker, R. R., and Robbins, F. P., Psychosomatic Case Book (E. W.), 249
Grollman, A., Pharmacology and Therapeutics, 2nd ed. (R. K.), 123
Harris, H., An Introduction to Human Biochemical Genetics (D. K.), 124
Haugaard, N., and Marsh, J. B., The Action of Insulin (C. Z.), 246
Haymaker, W., and Woodhall, B., Peripheral Nerve Injuries, 2nd ed. (M. S.), 115
Heepe, F., Die Unspezifischen Bluteiweissreaktionen (R. K.), 601
Herbut, P. A., Surgical Pathology, 2nd ed. (E. A.), 365
Hiller, A., Practical Clinical Chemistry (R. H.), 240
Hirst, L. F., The Conquest of Plague (R. K.), 238
Hochrein, M., and Hochrein-Schleicher, I., Leistungssteigerung: Leistung, Ubermudung, Gesunderhaltung, 3rd ed. (R. K.), 122
Hollinshead, W. H., Anatomy for Surgeons, Vol. 1, The Head and Neck (M. S.), 243
Ingraham, F. D., and Matson, D. D., Neurosurgery of Infancy and Childhood (M. S.), 242
Jaensch, P. A., Einfuhrung in die Augenheilkunde, 2nd ed. (W. P.), 117
Jaramillo-Arango, J., The British Contribution to Medicine (E. K.), 241
Jenkins, G. L., Christian, J. E., and Hager, G. P., Quantitative Pharmaceutical Chemistry, 4th ed. (C. Z.), 124
Kleine, H. O., Taschenbuch der Vitamintherapie in der Frauenheilkunde (J. W.), 120
Kolb, L. C., The Painful Phantom (O. E.), 604
Koller, E. K., and Katz, J. (Eds.), A Biblography of the World Literature on Blood Pressure, 1920–1950. Vols. I, II, and III (T. D.), 115
Korting, G., Zur Pathogenese des Endogenen Ekzems (H. B.), 490
Kux, E., Thorakoskopische Engriffe am Nervensystem (E. S.), 601
Lauffer, M. A., and Smith, K. M. (Eds.), Advances in Virus Research, Vol. 1 (C. Z.), 122
Lehmann, G., Praktische Arbeitsphysiologie (M. O.), 119
Lejeune, F., and Bunjes, W. E., German-English: English-German Dictionary for Physicians (R. K.), 239
Leupold, E., Die Bedeutung des Blutchemismus (J. S.), 245
Lewis, N. D. C., and Engle, B. (Eds.), Wartime Psychiatry (O. E.), 247
Luck, J. M. (Ed.), Annual Review of Biochemistry, Vol. 22 (C. Z.), 247
Luisada,, A. A., The Heart Beat (G. M.), 120
Lukens, F. D. W. (Ed.), Medical Uses of Cortisone (R. K.), 489
Mackay, R. P., Lewis, N. D. C., Bailey, P., and Sugar, O. (Eds.), Year Book of Neurology, Psychiatry and Neurosurgery (M. S.), 241
MacKenna, R. M. B. (Ed.), Modern Trends in Dermatology, Second Series (H. B.), 369
Mackie, T. T., Hunter, G. W., III, and Worth C. B., A Manual of Tropical Medicine, 2nd ed. (R. K.), 488
Martius, H., Die Kreuzschmerzen der Frau, 4th ed. (J. W.), 116
Massey, F. C. (Ed.), Clinical Cardiology (G. M.), 120
McKittrick, L. S., and Wheelock, F. C., Jr., Carcinoma of the Colon (J. B.), 242
Meaker, S. R., A Doctor Talks to Women (J. W.), 244
Means, J. H., Lectures on the Thyroid (R. K.), 237
Modell, W., and Schwartz, D. R., Handbook of Cardiology for Nurses, 2nd ed. (J. Z.), 370
Moloney, J. C., Understanding the Japanese Mind (A. G.), 240
Moore, H. G., Jr., and Harkins, H. N., The Billroth I Gastric Resection (R. T.), 248
Moritz, A. R., The Pathology of Trauma, 2nd ed. (E. A.), 365
Muhler, J. C., Hine, M. K., and Day, H. G., Preventive Dentistry (J. C.), 248
O'Malley, C. D., Michael Servetus (E. K.), 236
Ormsby, O. S., and Montgomery, H., Diseases of the Skin, 8th ed. (H. B.), 489
Papanicolaou, G. N., Atlas of Exfoliative Cytology (E. A.), 600
Parsons, L., and Ulfelder, H., An Atlas of Pelvic Operations (J. W.), 119
Paschkis, K. E., Rakoff, A. E., and Cantarow, A., Clinical Endocrinology (W. P.), 247
Pearson, G. H. J., Psychoanalysis and the Education of the Child (O. E.), 368
Pinsent, R. J. F. H., An Approach to General Practice (W. S.), 239
Pitkin, G. P. (Southworth, J. L., Hingson, R. A., and Pitkin, W. M., Eds.). Conduction Anesthesia, 2nd ed. (L. K.), 115
Pneumoconiosis Abstracts, Vol. 1 (R. K.), 117 Vol. 2 (R. K.), 601
Podolsky, E., The Jealous Child (O. E.), 124
Podolsky, E., Music Therapy (O. E.), 238
Popper, H., and Kushner, D. S., (Eds.), Clinical Pathologic Conferences of Cook County Hospital Vol. 1. Cardiovascular-Renal Problems (T. D.), 599
Pratt, G. H., Cardiovascular Surgery (G. R.), 247
Pratt, R., and Dufrenoy, J., Antibiotics, 2nd ed. (C. Z.), 366
Proceedings of the Society for the Study of Fertility, Liverpool Conferences, 1953 (J. W.), 604
Pulaski, E. J., Surgical Infections (H. C.), 246

Randall, J. T. (Ed.), Nature and Structure of Collagen (E. A.), 488
Reddish, G. F. (Ed.), Antiseptics, Disinfectants, Fungicides, and Chemical and Physical Sterilization (E. S.), 487
Reich, N. E., The Uncommon Heart Diseases (T. D.), 599
Reiner, M. (Ed.), Standard Methods of Clinical Chemistry, Vol. 1 (C. Z.), 124
Rhinehart, D. A., Roentgenographic Technique, 4th ed. (H. S.), 370
Robinson, F. A., Antibiotics (W. S.), 250
Roth, O. A., and Schwenkenbecher, W. (Eds.), Streicher and Sandkuhler's Klinische Zytologie (E. K.), 369
Rothman, S., Physiology and Biochemistry of the Skin (H. B.), 365
Rusk, H. A., and Taylor, E. J., Living with a Disability (R. K.), 123
Scherf, D., and Schott, A., Extrasystoles and Allied Arrhythmias (T. D.), 115
Schilder, P. (Rapaport, D., Ed. and Translator), Medical Psychology (O. E.), 118
Schulten, H., Lehrbuch der klinischen Hamatologie, 5th ed. (C. Z.), 365
Scott, W. G., Planning Guide for Radiologic Installations (H. S.), 248
Sebrell, W. H., Jr., and Harris, R. S., The Vitamins: Chemistry, Physiology, Pathology, Vol. 1 (R. K.), 603
Seed, L., and Fields, T., Treatment of Toxic Goiter with Radioactive Iodine (R. R.), 237
Selye, H., and Horava, A., Third Annual Report on Stress (W. P.), 249
Serbein, O. N., Jr., Paying for Medical Care in the United States (R. K.), 240
Seward C., Bedside Diagnosis, 2nd ed. (H. B.), 368
Siebeck, R., Medizin in Bewegung, 2nd ed. (R. K.), 238
Sigerist, H. E., Grosse Artze, 3rd ed. (R. K.), 237
Simmons, J. S., Whayne, T. F., Anderson, G. W., Horack, H. M., Thomas, R. A., and Collaborators, Global Epidemiology, Vol. 3. The Near and Middle East (R. K.), 116
Simmons, L. W., and Wolff, H. G., Social Science in Medicine (O. E.), 367
Smith, P. E., and Copenhaver, W. M. (Revisers), Bailey's Textbook of Histology, 13th ed. (N. B.), 250
Soskin, S., and Levine, R., Carbohydrate Metabolism, 2nd ed. (C. Z.), 245
Spellberg, M. A., Diseases of the Liver (H. S.), 243
Spencer, S. M., Wonders of Modern Medicine (R. K.), 122
Steele, J. M. (Ed.), Methods in Medical Research, Vol. 6 (C. Z.), 367
Stevenson, G. S. (Ed.), Administrative Medicine, Transactions of the First Conference (H. B.), 124
Stevenson, L. G., Nobel Prize Winners in Medicine and Physiology, 1901–1950 (R. K.), 602
Stodtmeister, R., Sandkuhler, S., and Laur, A., Osteosklerose und Knochenmarkfibrose (C. Z.), 241
Sturgis, C. C., Hypersplenism (C. Z.), 119
Sullivan, H. S. (Perry, H. S., and Gawel, M. L., Eds.), The Psychiatric Interview (O. E.), 366
Texon, M., Heart Disease and Industry (T. D.), 490
Uhlenhuth, E., and Hunter, D. T., Problems in the Anatomy of the Pelvis (D. K.), 236
Underwood, E. A. (Ed.), Science, Medicine and History (R. K.), 490
Vine, J., The Theory of Wholes in Chemistry (R. H.), 237
Waksman, S. A., and Lechevalier, H. A., Guide to the Classification and Identification of the Actinomycetes and their Antibiotics (E. S.), 123
Wartman, W. B. (Ed.), The Year Book of Pathology and Clinical Pathology, 1953–1954 (C. Z.), 369
Weber, E. M. W., Schemata der Leitungsbahnen des Menschen (E. S.), 604
Wechsler, I. R., and Brown, P. (Eds.), Evaluating Research and Development (C. Z.), 121
Whittaker, E., A History of the Theories of Aether and Electricity (G. H.), 241
Wiener, A. S., Rh-Hr Blood Types. Applications in Clinical and Legal Medicine and Anthropology (C. Z.), 236
Wolf, H. J., Einfuhrung in die innere Medizin, 5th ed. (R. K), 122
Wolf-Heidegger, G., Atlas der Systematischen Anatomie des Menschen, Vol. 1 (J. H.), 599
World Health Organization Monograph Series, No. 20, Influenza (M. K.), 245
World Health Organization Official Records No. 51, The Work of WHO, 1953 (R. K.), 603
Yoffey, J. M. (Ed.), The Suprarenal Cortex (C. Z.), 117
Zentralblatt fur Veterinarmedizin, Vol. 1, Nos. 1 and 2 (R. K.), 237
Zilboorg, G., The Psychology of the Criminal Act and Punishment (O. E.), 244
Ziskind, E., Psychophysiologic Medicine (O. E.), 246

Reynolds, T. B., *see* Reece, J. M., 554
Reynolds W. E., *see* Kowalski, H. J. *et al.*, 275
Rheumatoid arthritis, amyloidosis complicating, 554
Rhoads, C. P., *see* Burchenal, J. H., *et al.*, 371
Rogers, S., *see* Moyer, J. H., *et al.*, 174
Rosen, I., *see* Welch. G. E., *et al.*, 643
Rubin, M., *see* Seven, M. J., *et al.*, 646
Russek, H. I., and Zohman, B. L., Selection of patients for anticoagulant therapy in acute myocardial infarction, 133
Rutstein, D. D., *see* Kowalski, H. J., *et al.*, 275

S

Salmonella cholerae suis, 525
Sanchez, G. C., *see* Ingelfinger, F. J., *et al.*, 417
Saphra, I., and Wassermann, M., *Salmonella cholerae suis*, 525
Schaaf, M., and Kyle, L. H., Measurement of per cent renal phosphorus reabsorption in diagnosis of hyperparathyroidism, 262
Schiffer, L. M., *see* Cardillo, T. E., *et al.*, 214
Schroeder, H. A., *see* Perry, H. M., Jr., *et al.*, 396, 405
Secretion, gastric, and stress in man: mechanisms involved in insulin hypoglycemia, 630
Secretions, tracheobronchial, of patients with poliomyelitis, effect of proteolytic enzymes on physical and chemical characteristics of, 426

Seneca, H., and Bergendahl, E., Synergistic amebicidal effect of tetracycline, oxytetracycline and carbomycin on cultures of *Endameba histolytica*, 16
Sera and urines of patients with severe proteinurias, complement components in, 448
Serpasil (reserpine) in hypertension, 21
Serum and muscle electrolytes, comparison of tolerance of normal dog and dog with myocardial infarction to organic mercurial (Mercurophylline), 282
citric acid in Paget's disease, 301
reaction, anamnestic, evaluation of, in certain febrile illnesses, 520
Seven, M. J., Gottlieb, H., Israel, H. L., Reinhold J. G., and Rubin, M,. N-hydroxethylethylenediamine triacetic acid, Versenol, in hemochromatosis, 646
Shay, H., and Sun, D. C. H., Stress and gastric secretion in man: mechanisms involved in insulin hypoglycemia, 630
Sherman, A. I., and Arneson, A. N., Carcinoma of endometrium, 701
Shoulberg, J. M., *see* Kowalski, H. J., *et al.*, 275
Siebens, A. A., *see* Flynn, J. E., *et al.*, 673
Siegel, I., *see* Havens, W. P., Jr., *et al.*, 251
Silverman, A. C., *see* Müller, O. H., *et al.*, 510
Simons, R. L., Hepatic tests in metastatic carcinoma of liver, 312
Smith, C. P., *see* Moyer, J. H., *et al.*, 563
Snyder, H., *see* Moyer, J. H., *et al.*, 563
Sodium chromate, radioactive, to evaluate life span of red blood cell in health and certain hematologic disorders, 40
excretion in advanced renal disease, 306
Soloff, L. A., and Zatuchni, J., Cardiac enlargement following mitral commissurotomy, 57
Spurr, C. L., Ford, R. V., Moyer, J. H., Garson, E., and Weller, G., Effect of probenecid (Benemid) on phosphate excretion and other metabolic processes, 256
see Moyer, J. H., *et al.*, 174
Steiger, W. A., *see* Zarafonetis, C. J. D., *et al.*, 1
Steinfield E., and Beizer, L. H., Myeloid metaplasia as sequela of polycythemia, 388
Stenosis, mitral, natural history, functional capacity and exercise tolerance of unoperated patients with, 605
Stomach, greater curvature of, incidence of perforation in benign peptic ulcer of, 506
Streptokinase-streptodornase or trypsin, for therapy and prevention of atelectasis, 432
Stress and gastric secretion in man: mechanisms involved in insulin hypoglycemia, 630
Subdural hematoma in infancy; convulsions, anorexia and irritability, evidence of, 540
Sulfadiazine and eleven antibiotics, *in vitro* susceptibility of meningococci to, 534
Sulfhydryl content of human leukocytes and erythrocytes, 73
Sun, D. C. H., *see* Shay, H., 630
Suppository, mercurial rectal, diuretic effect and local tolerance of new type of, 440
Susceptibility, *in vitro*, of meningococci to eleven antibiotics and sulfadiazine, 534
Sykes, M. P., *see* Burchenal, J. H., *et al.*, 371
Syndrome, Fanconi, and its clinical variants, 378
Parkinson's, drug therapy of, 97

T

Tan, C. T. C., *see* Burchenal, J. H., *et al.*, 371
Tests, hepatic, in metastatic carcinoma of liver, 312
Tetracycline: clinical and pharmacologic studies, 164
oxytetracycline and carbomycin, synergistic amebicidal effect of, on cultures of *Endameba histolytica*, 16
Thomas, E. B., *see* Benda, C. E., *et al.*, 668
Thrombocytopenic purpura, idiopathic, compounds E and F and ACTH in, 1
Thyroid function in myotonia dystrophica, 668
Tolerance of normal dog and dog with myocardial infarction, comparison of, to organic mercurial (Mercurophylline): study of serum and muscle electrolytes, 282
Torregro[illegible] M. V., Ramos-Morales, F., Pons, E., Jr., de Andino, A. M., Jr., and Diaz Rivera, R. S., Circulating antithromboplastic anticoagulant: ineffectiveness of cortisone and corticotropin, 269
Tortuosity, aortic, value of lateral ballistocardiograms in differentiating, from myocardial dysfunction, 125
Tracheobronchial secretions of patients with poliomyelitis, effect of proteolytic enzymes on physical and chemical characteristics of, 426
Trauma, distant, lesions of retina and optic nerve secondary to, 226
Trypsin or streptokinase-stretodornase, for therapy and prevention of atelectasis, 432
Tuberculosis, active pulmonary, and Addison's disease, treatment of coexisting, 491
Tumor of pituitary, concomitance of multiple adenomas of parathyroids and pancreatic islets with: syndrome with familial incidence, 190

U

Ulcer, benign peptic, of greater curvature of stomach, incidence of perforation in, 506
Unoperated patients with mitral stenosis, natural history, functional capacity and exercise tolerance of, 605
Uremia and acidosis due to advanced renal disease, uptake of base in, 656
Urine and blood, levels of agents in: hypertension control by hyphex, 405
Urines and sera of patients with severe proteinurias, complement components in, 448

V

Valentine, W. N., *see* Hardin, B., *et al.*, 73
Van Horne, R., *see* Kramer, L. B., *et al.*, 614
Vasculitis, nodular, 469
Venous blood, portal and hepatic, microbiologic studies of, in man, 298
system, portal and hepatic venule in man, simultaneous pressure measurements in, 643
Venule, hepatic, and portal venous system in man, simultaneous pressure measurements in, 643
Versenol, N-hydroxethylethylenediamine triacetic acid, in hemochromatosis, 646
Vestibule, gastroesophageal, normal function and role in cardiospasm and gastroesophageal reflux, 417

W

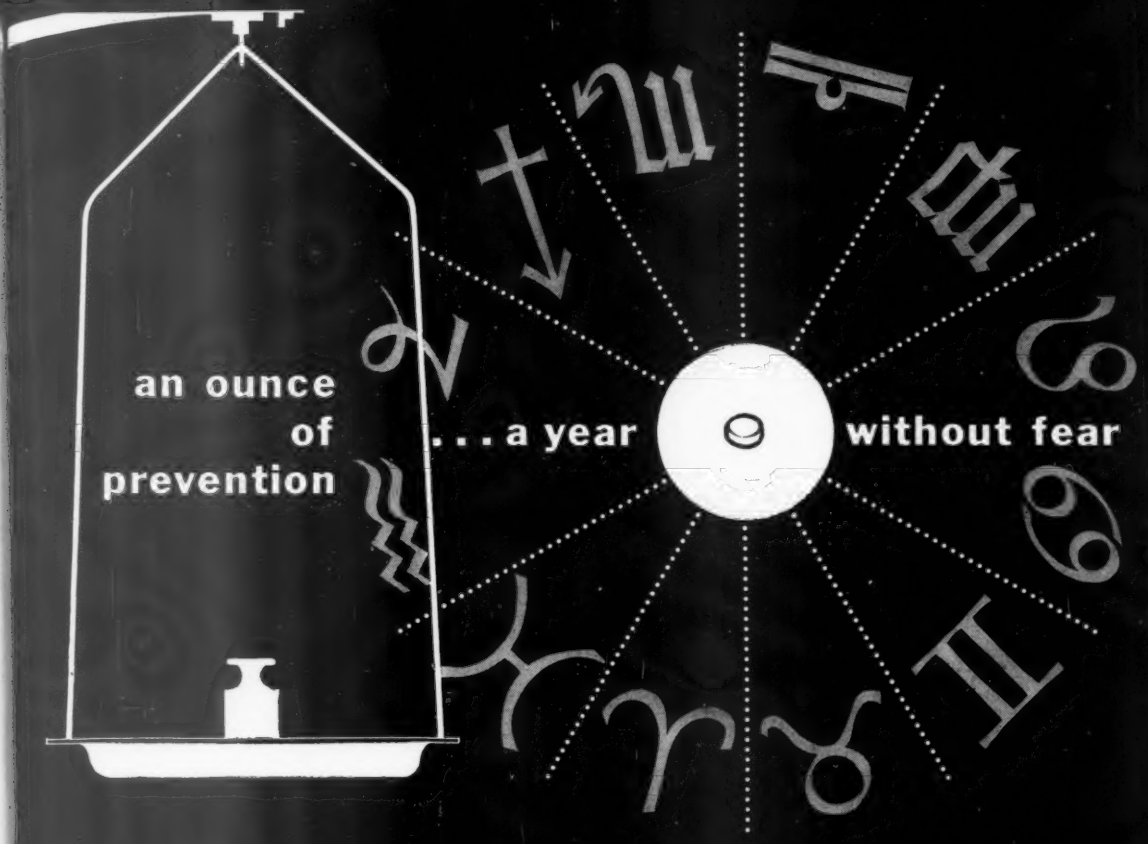
Waddington, W. S., Bergy, G. G., Nielsen, R. L., and Kirby, W. M. M., Tetracycline: clinical and pharmacologic studies, 164
Wagener, H. P., Lesions of retina and optic nerve secondary to distant trauma, 226
Walford, R. L., *see* Manning, P. R., 652
Wassermann, M., *see* Saphra, I., 525
Weiner, M., Chenkin, T., and Burns, J. J., Metabolic transformation and effects of phenylbutazone in hepatic disease, 36
Weiss, W., Eisenberg, G. M., Alexander, J. D., Jr., and Flippin, H. F., Klebsiella pulmonary disease, 148
Welch, G. E., Emmett, R., Craighead, C. C., Hoeffler, G., Brown, D. C., and Rosen, I., Simultaneous pressure measurements in hepatic venule and portal venous system in man, 643
Weller, G., *see* Spurr, C. L., *et al.*, 256
Wenk, E. J., *see* Lange, K., 448, 454
Williams, S. F., *see* Flynn, J. E., *et al.*, 673
Willson, J. K. V., *see* Gould, D. M., 586
Wilson, G. W., *see* Read, R. C., *et al.*, 40
Wounded patients, seriously, capacity of, to produce antibody, 251

Y

Yüceoglu, M., *see* Burchenal, J. H., *et al.*, 371

Z

Zarafonetis, C. J. D., and Colville, V. F., Forssman-like behavior of cold hemagglutinins for sheep erythrocytes, 461
Steiger, W. A., and Cary, S. K., Compounds E and F, and ACTH in idiopathic thrombocytopenic purpura, 1
Zatuchni, J., *see* Soloff, L. A., 57
Zohman, B. L., *see* Russek, H. I., 133



for the patient with angina pectoris

With Peritrate, the long-acting coronary vasodilator, an ounce of prevention (28,350 mg. of Peritrate) lasts a full year or longer, since only 10 or 20 mg. are needed to protect most patients for 4 to 5 hours. Yet, no arithmetic formula can adequately define the effectiveness of Peritrate in providing dramatic relief from pain and from the fear of anginal attacks.

According to tests made by Russek and coworkers, Peritrate is unexcelled in exerting a prolonged prophylactic effect in angina pectoris. The results achieved ". . . were comparable to those obtained with glyceryl trinitrate (nitroglycerin), but the duration of action was considerably more prolonged."[1] Patients on Peritrate generally exhibit significant EKG improvement,[1,2] and their need for nitroglycerin is often reduced.[3] A continuing year-round schedule of 10 or 20 mg. 4 times a day will usually:

1. reduce the number of attacks (in 8 out of 10 patients[2,3]);
2. reduce the severity of attacks not prevented.

Available in both 10 mg. and 20 mg. tablets and, for extended night-long protection, in Enteric Coated tablets (10 mg.).

1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

Peritrate®

tetranitrate

(BRAND OF PENTAERYTHRITOL TETRANITRATE)

WARNER-CHILCOTT

New

For ESSENTIAL HYPERTENSION

an alliance of the classic and contemporary . . .

THEOMINAL® R.S.

(Theominal with Rauwolfia serpentina)

Combines for synergistic action:

Theobromine	*(5 grains) 0.32 Gm.*
Luminal® (pioneer brand of phenobarbital)	*(1/6 grain) 10 mg.*
Rauwolfia serpentina alkaloids (alseroxylon fraction)	***1.5 mg.***

Theominal itself has been widely prescribed for essential hypertension for several decades. The addition of Rauwolfia serpentina alkaloids—purified alseroxylon fraction—to the well established Theominal formula represents a substantial improvement.

With the use of Theominal R.S., objective and subjective improvement can be obtained in a large percentage of hypertensive patients. There is mild and gradual but sustained reduction of excessive blood pressure and pulse rate to near normal levels. Striking symptomatic improvement occurs concurrently: alleviation of congestive headache, vertigo, dyspnea, nervous irritability, apprehension and insomnia.

With Theominal R.S. medication the antihypertensive action of Luminal and theobromine may be evident in a few days, whereas a week or more may elapse before the Rauwolfia component exhibits its maximum effectiveness. However, the sense of well being due to Rauwolfia is experienced within a few days of medication and usually precedes the development of the maximum antihypertensive effect. Theominal R.S. is well tolerated.

DOSAGE: The usual dose of Theominal R.S. is 1 tablet two or three times daily. When improvement has been maintained for a time, the dose may be reduced or medication suspended occasionally until its resumption is indicated.

HOW SUPPLIED: Theominal R.S. is supplied in bottles of 100 tablets.

WINTHROP

Winthrop-Stearns INC.
New York 18, N. Y. Windsor, Ont.

Theominal and Luminal, trademarks reg. U. S. Pat. Off.